

WO 03/091232

PCT/GB03/01742

CHEMICAL COMPOUNDS

This invention relates to benzothiadiazepine derivatives, or pharmaceutically acceptable salts, solvates, solvates of such salts and prodrugs thereof. These 5 benzothiadiazepines possess ileal bile acid transport (IBAT) inhibitory activity and accordingly have value in the treatment of disease states associated with hyperlipidaemic conditions and they are useful in methods of treatment of a warm-blooded animal, such as man. The invention also relates to processes for the manufacture of said benzothiadiazepine derivatives, to pharmaceutical compositions containing them and to their use in the 10 manufacture of medicaments to inhibit IBAT in a warm-blooded animal, such as man.

It is well-known that hyperlipidaemic conditions associated with elevated concentrations of total cholesterol and low-density lipoprotein cholesterol are major risk factors for cardiovascular atherosclerotic disease (for instance "Coronary Heart Disease: Reducing the Risk; a Worldwide View" Assman G., Carmena R. Cullen P. *et al*; Circulation 15 1999, 100, 1930-1938 and "Diabetes and Cardiovascular Disease: A Statement for Healthcare Professionals from the American Heart Association" Grundy S, Benjamin L, Burke G., *et al*; Circulation, 1999, 100, 1134-46). Interfering with the circulation of bile acids within the lumen of the intestinal tracts is found to reduce the level of cholesterol. Previous established therapies to reduce the concentration of cholesterol involve, for instance, treatment with 20 HMG-CoA reductase inhibitors, preferably statins such as simvastatin and fluvastatin, or treatment with bile acid binders, such as resins. Frequently used bile acid binders are for instance cholestyramine and colestipol. One recently proposed therapy ("Bile Acids and Lipoprotein Metabolism: a Renaissance for Bile Acids in the Post Statin Era" Angelin B, Eriksson M, Rudling M; Current Opinion on Lipidology, 1999, 10, 269-74) involved the 25 treatment with substances with an IBAT inhibitory effect.

Re-absorption of bile acid from the gastro-intestinal tract is a normal physiological process which mainly takes place in the ileum by the IBAT mechanism. Inhibitors of IBAT can be used in the treatment of hypercholesterolaemia (see for instance "Interaction of bile acids and cholesterol with nonsystemic agents having hypocholesterolaemic properties", 30 Biochimica et Biophysica Acta, 1210 (1994) 255- 287). Thus, suitable compounds having such inhibitory IBAT activity are also useful in the treatment of hyperlipidaemic conditions. Compounds possessing such IBAT inhibitory activity have been described, see for instance the compounds described in WO 93/16055, WO 94/18183, WO 94/18184, WO 96/05188,

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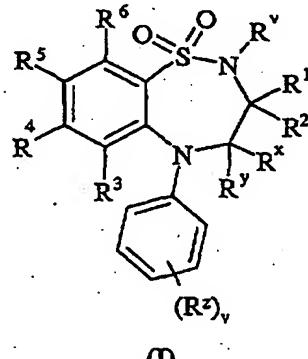
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WO 96/08484, WO 96/16051, WO 97/33882, WO 98/38182, WO 99/35135, WO 98/40375, WO 99/35153, WO 99/64409, WO 99/64410, WO 00/01687, WO 00/47568, WO 00/61568, WO 01/68906, DE 19825804, WO 00/38725, WO 00/38726, WO 00/38727, WO 00/38728, WO 00/38729, WO 01/68906 and EP 0 864 582.

5 A further aspect of this invention relates to the use of the compounds of the invention in the treatment of dyslipidemic conditions and disorders such as hyperlipidaemia, hypertriglyceridemia, hyperbetalipoproteinemia (high LDL), hyperprebetalipoproteinemia (high VLDL), hyperchylomicronemia, hypolipoproteinemia, hypercholesterolemia, hyperlipoproteinemia and hypoalphalipoproteinemia (low HDL). In addition, these
10 compounds are expected to be useful for the prevention and treatment of different clinical conditions such as atherosclerosis, arteriosclerosis, arrhythmia, hyper-thrombotic conditions, vascular dysfunction, endothelial dysfunction, heart failure, coronary heart diseases, cardiovascular diseases, myocardial infarction, angina pectoris, peripheral vascular diseases, inflammation of cardiovascular tissues such as heart, valves, vasculature, arteries and veins,
15 aneurisms, stenosis, restenosis, vascular plaques, vascular fatty streaks, leukocytes, monocytes and/or macrophage infiltration, intimal thickening, medial thinning, infectious and surgical trauma and vascular thrombosis, stroke and transient ischaemic attacks.

The present invention is based on the discovery that certain benzothiadiazepine compounds surprisingly inhibit IBAT. Such properties are expected to be of value in the
20 treatment of disease states associated with hyperlipidaemic conditions.

Accordingly, the present invention provides a compound of formula (I):



(I)

wherein:

25 R^v is selected from hydrogen or C₁₋₆alkyl;

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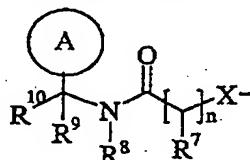
One of R^1 and R^2 are selected from hydrogen or C_{1-6} alkyl and the other is selected from C_{1-6} alkyl;

R^x and R^y are independently selected from hydrogen, hydroxy, amino, mercapto, C_{1-6} alkyl, C_{1-6} alkoxy, $N-(C_{1-6}$ alkyl)amino, $N,N-(C_{1-6}$ alkyl)₂amino, C_{1-6} alkylS(O)_a wherein a is 0 to 2;

R^z is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, $N-(C_{1-6}$ alkyl)amino, $N,N-(C_{1-6}$ alkyl)₂amino, C_{1-6} alkanoylamino, $N-(C_{1-6}$ alkyl)carbamoyl, $N,N-(C_{1-6}$ alkyl)₂carbamoyl, C_{1-6} alkylS(O)_a wherein a is 0 to 2, C_{1-6} alkoxycarbonyl, $N-(C_{1-6}$ alkyl)sulphamoyl and $N,N-(C_{1-6}$ alkyl)₂sulphamoyl;

v is 0-5;

one of R^4 and R^5 is a group of formula (IA):



(IA)

R^3 and R^6 and the other of R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, $N-(C_{1-6}$ alkyl)amino, $N,N-(C_{1-6}$ alkyl)₂amino, C_{1-6} alkanoylamino, $N-(C_{1-6}$ alkyl)carbamoyl, $N,N-(C_{1-6}$ alkyl)₂carbamoyl, C_{1-6} alkylS(O)_a wherein a is 0 to 2, C_{1-6} alkoxycarbonyl, $N-(C_{1-6}$ alkyl)sulphamoyl and $N,N-(C_{1-6}$ alkyl)₂sulphamoyl; wherein R^3 and R^6 and the other of R^4 and R^5 may be optionally substituted on carbon by one or more R^{17} ;

X is $-O-$, $-N(R^a)-$, $-S(O)_b-$ or $-CH(R^a)-$; wherein R^a is hydrogen or C_{1-6} alkyl and b is 0-2;

Ring A is aryl or heteroaryl; wherein Ring A is optionally substituted on carbon by one or more substituents selected from R^{18} ;

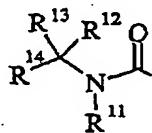
R^7 is hydrogen, C_{1-6} alkyl, carbocyclyl or heterocyclyl; wherein R^7 is optionally substituted on carbon by one or more substituents selected from R^{19} ; and wherein if said heterocyclyl contains an $-NH-$ group, that nitrogen may be optionally substituted by a group selected from R^{20} ;

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R^8 is hydrogen or C_{1-6} alkyl;

R^9 is hydrogen or C_{1-6} alkyl;

R^{10} is hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy, 5 C_{1-10} alkanoyl, C_{1-10} alkanoyloxy, $N-(C_{1-10}$ alkyl)amino, $N,N-(C_{1-10}$ alkyl)₂amino, $N,N,N-(C_{1-10}$ alkyl)₃ammonio, C_{1-10} alkanoylamino, $N-(C_{1-10}$ alkyl)carbamoyl, $N,N-(C_{1-10}$ alkyl)₂carbamoyl, C_{1-10} alkylS(O)_a wherein a is 0 to 2, $N-(C_{1-10}$ alkyl)sulphamoyl, $N,N-(C_{1-10}$ alkyl)₂sulphamoyl, $N-(C_{1-10}$ alkyl)sulphamoylamino, $N,N-(C_{1-10}$ alkyl)₂sulphamoylamino, C_{1-10} alkoxycarbonylamino, carbocyclyl, 10 carbocyclyl C_{1-10} alkyl, heterocyclyl, heterocyclyl C_{1-10} alkyl, carbocyclyl-(C_{1-10} alkylene)_p- R^{21} -(C_{1-10} alkylene)_q- or heterocyclyl-(C_{1-10} alkylene)_r- R^{22} -(C_{1-10} alkylene)_s-; wherein R^{10} is optionally substituted on carbon by one or more substituents selected from R^{23} ; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from 15 R^{24} ; or R^{10} is a group of formula (IB):



(IB)

wherein:

R^{11} is hydrogen or C_{1-6} alkyl;

R^{12} and R^{13} are independently selected from hydrogen, halo, carbamoyl, sulphamoyl, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkanoyl, $N-(C_{1-10}$ alkyl)carbamoyl, $N,N-(C_{1-10}$ alkyl)₂carbamoyl, C_{1-10} alkylS(O)_a wherein a is 0 to 2, $N-(C_{1-10}$ alkyl)sulphamoyl, $N,N-(C_{1-10}$ alkyl)₂sulphamoyl, $N-(C_{1-10}$ alkyl)sulphamoylamino, $N,N-(C_{1-10}$ alkyl)₂sulphamoylamino, carbocyclyl or heterocyclyl; wherein R^{12} and R^{13} may be independently optionally substituted on carbon by one or more substituents selected from R^{25} , 20 and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{26} ;

R^{14} is selected from hydrogen, halo, carbamoyl, sulphamoyl, hydroxyaminocarbonyl, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkanoyl, $N-(C_{1-10}$ alkyl)carbamoyl, 25 $N,N-(C_{1-10}$ alkyl)₂carbamoyl, C_{1-10} alkylS(O)_a wherein a is 0 to 2, $N-(C_{1-10}$ alkyl)sulphamoyl,

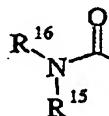
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N,N-(C₁₋₁₀alkyl)₂sulphamoyl, N-(C₁₋₁₀alkyl)sulphamoylamino,

N,N-(C₁₋₁₀alkyl)₂sulphamoylamino, carbocyclyl, carbocyclylC₁₋₁₀alkyl, heterocyclyl,

heterocyclylC₁₋₁₀alkyl, carbocyclyl-(C₁₋₁₀alkylene)_p-R²⁷-(C₁₋₁₀alkylene)_q- or

heterocyclyl-(C₁₋₁₀alkylene)_r-R²⁸-(C₁₋₁₀alkylene)_s; wherein R¹⁴ may be optionally substituted
 5 on carbon by one or more substituents selected from R²⁹; and wherein if said heterocyclyl
contains an -NH- group, that nitrogen may be optionally substituted by a group selected from
R³⁰; or R¹⁴ is a group of formula (IC):



(IC)

10 R¹⁵ is hydrogen or C₁₋₆alkyl; and R¹⁶ is hydrogen or C₁₋₆alkyl; wherein R¹⁶ may be
optionally substituted on carbon by one or more groups selected from R³¹; or R¹⁵ and R¹⁶
together with the nitrogen to which they are attached form a heterocyclyl; wherein said
heterocyclyl may be optionally substituted on carbon by one or more R³⁷; and wherein if said
heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group
 15 selected from R³⁸;

n is 1-3; wherein the values of R⁷ may be the same or different;

R¹⁷, R¹⁸, R¹⁹, R²³, R²⁵, R²⁹, R³¹ and R³⁷ are independently selected from halo, nitro,
cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C₁₋₁₀alkyl,
C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₁₋₁₀alkoxy, C₁₋₁₀alkanoyl, C₁₋₁₀alkanoyloxy, N-(C₁₋₁₀alkyl)amino,
 20 N,N-(C₁₋₁₀alkyl)₂amino, N,N,N-(C₁₋₁₀alkyl)₃ammonio, C₁₋₁₀alkanoylamino,
N-(C₁₋₁₀alkyl)carbamoyl, N,N-(C₁₋₁₀alkyl)₂carbamoyl, C₁₋₁₀alkylS(O)_a wherein a is 0 to 2,
N-(C₁₋₁₀alkyl)sulphamoyl, N,N-(C₁₋₁₀alkyl)₂sulphamoyl, N-(C₁₋₁₀alkyl)sulphamoylamino,
N,N-(C₁₋₁₀alkyl)₂sulphamoylamino, C₁₋₁₀alkoxycarbonylamino, carbocyclyl,
carbocyclylC₁₋₁₀alkyl, heterocyclyl, heterocyclylC₁₋₁₀alkyl,
 25 carbocyclyl-(C₁₋₁₀alkylene)_p-R³²-(C₁₋₁₀alkylene)_q- or
heterocyclyl-(C₁₋₁₀alkylene)_r-R³³-(C₁₋₁₀alkylene)_s;- wherein R¹⁷, R¹⁸, R¹⁹, R²³, R²⁵, R²⁹, R³¹
and R³⁷ may be independently optionally substituted on carbon by one or more R³⁴; and
wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally
substituted by a group selected from R³⁵;

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R^{21} , R^{22} , R^{27} , R^{28} , R^{32} or R^{33} are independently selected from $-O-$, $-NR^{36}-$, $-S(O)_x-$, $-NR^{36}C(O)NR^{36}-$, $-NR^{36}C(S)NR^{36}-$, $-OC(O)N=C-$, $-NR^{36}C(O)-$ or $-C(O)NR^{36}-$; wherein R^{36} is selected from hydrogen or C_{1-6} alkyl, and x is 0-2;

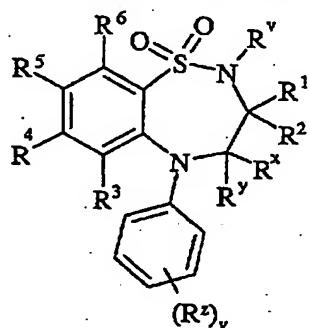
5 p , q , r and s are independently selected from 0-2;

R^{34} is selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, formyl, acetyl, formamido, acetylarnino, acetoxy, methylarnino, dimethylarnino, N -methylcarbamoyl, N,N -dimethylcarbamoyl, methylthio, methylsulphinyl, mesyl, N -methylsulphamoyl, N,N -dimethylsulphamoyl, N -methylsulphamoylarnino and

10 N,N -dimethylsulphamoylarnino;

R^{20} , R^{24} , R^{26} , R^{30} , R^{35} and R^{38} are independently selected from C_{1-6} alkyl, C_{1-6} alkanoyl, C_{1-6} alkylsulphonyl, C_{1-6} alkoxycarbonyl, carbamoyl, $N-(C_{1-6}$ alkyl)carbamoyl, $N,N-(C_{1-6}$ alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

15 A further aspect of the invention provides a compound of formula (I):



(I)

wherein:

R^v is selected from hydrogen or C_{1-6} alkyl;

20 One of R^1 and R^2 are selected from hydrogen or C_{1-6} alkyl and the other is selected from C_{1-6} alkyl;

R^x and R^y are independently selected from hydrogen, hydroxy, amino, mercapto, C_{1-6} alkyl, C_{1-6} alkoxy, $N-(C_{1-6}$ alkyl)arnino, $N,N-(C_{1-6}$ alkyl)₂arnino, C_{1-6} alkylS(O)_a wherein a is 0 to 2;

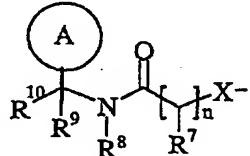
25 R^z is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy,

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N-(C₁₋₆alkyl)amino, *N,N*-(C₁₋₆alkyl)₂amino, C₁₋₆alkanoylamino, *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkylS(O)_a wherein a is 0 to 2, C₁₋₆alkoxycarbonyl, *N*-(C₁₋₆alkyl)sulphamoyl and *N,N*-(C₁₋₆alkyl)₂sulphamoyl;

v is 0-5;

5 one of R⁴ and R⁵ is a group of formula (IA):



(IA)

R³ and R⁶ and the other of R⁴ and R⁵ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, *N*-(C₁₋₆alkyl)amino, *N,N*-(C₁₋₆alkyl)₂amino, C₁₋₆alkanoylamino, *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkylS(O)_a wherein a is 0 to 2, C₁₋₆alkoxycarbonyl, *N*-(C₁₋₆alkyl)sulphamoyl and *N,N*-(C₁₋₆alkyl)₂sulphamoyl; wherein R³ and R⁶ and the other of R⁴ and R⁵ may be optionally substituted on carbon by one or more R¹⁷;

15 X is -O-, -N(R^a)-, -S(O)_b- or -CH(R^b)-; wherein R^a is hydrogen or C₁₋₆alkyl and b is 0-2;

Ring A is aryl or heteroaryl; wherein Ring A is optionally substituted on carbon by one or more substituents selected from R¹⁸;

20 R⁷ is hydrogen, C₁₋₆alkyl, carbocyclyl or heterocyclyl; wherein R⁷ is optionally substituted on carbon by one or more substituents selected from R¹⁹; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R²⁰;

R⁸ is hydrogen or C₁₋₆alkyl;

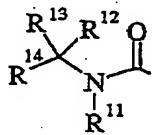
R⁹ is hydrogen or C₁₋₆alkyl;

25 R¹⁰ is hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₁₋₁₀alkoxy, C₁₋₁₀alkanoyl, C₁₋₁₀alkanoyloxy, *N*-(C₁₋₁₀alkyl)amino, *N,N*-(C₁₋₁₀alkyl)₂amino, *N,N,N*-(C₁₋₁₀alkyl)₃ammonio, C₁₋₁₀alkanoylamino, *N*-(C₁₋₁₀alkyl)carbamoyl, *N,N*-(C₁₋₁₀alkyl)₂carbamoyl, C₁₋₁₀alkylS(O)_a wherein a is 0 to 2, *N*-(C₁₋₁₀alkyl)sulphamoyl,

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N,N-(C₁₋₁₀alkyl)₂sulphamoyl, N-(C₁₋₁₀alkyl)sulphamoylamino,
N,N-(C₁₋₁₀alkyl)₂sulphamoylamino, C₁₋₁₀alkoxycarbonylamino, carbocyclyl,
carbocyclylC₁₋₁₀alkyl, heterocyclyl, heterocyclylC₁₋₁₀alkyl,
carbocyclyl-(C₁₋₁₀alkylene)_p-R²¹-(C₁₋₁₀alkylene)_q- or

5 *heterocyclyl-(C₁₋₁₀alkylene)_r-R²²-(C₁₋₁₀alkylene)_s-; wherein R¹⁰ is optionally substituted on carbon by one or more substituents selected from R²³; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R²⁴; or R¹⁰ is a group of formula (IB):*



(IB)

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wherein:

R¹¹ is hydrogen or C₁₋₆alkyl;

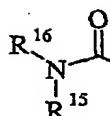
R¹² and R¹³ are independently selected from hydrogen, halo, carbamoyl, sulphamoyl, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₁₋₁₀alkanoyl, N-(C₁₋₁₀alkyl)carbamoyl,

15 N,N-(C₁₋₁₀alkyl)₂carbamoyl, C₁₋₁₀alkylS(O)_a wherein a is 0 to 2, N-(C₁₋₁₀alkyl)sulphamoyl, N,N-(C₁₋₁₀alkyl)₂sulphamoyl, N-(C₁₋₁₀alkyl)sulphamoylamino, N,N-(C₁₋₁₀alkyl)₂sulphamoylamino, carbocyclyl or heterocyclyl; wherein R¹² and R¹³ may be independently optionally substituted on carbon by one or more substituents selected from R²⁵; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R²⁶;

20 R¹⁴ is selected from hydrogen, halo, carbamoyl, sulphamoyl, hydroxyaminocarbonyl, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₁₋₁₀alkanoyl, N-(C₁₋₁₀alkyl)carbamoyl, N,N-(C₁₋₁₀alkyl)₂carbamoyl, C₁₋₁₀alkylS(O)_a wherein a is 0 to 2, N-(C₁₋₁₀alkyl)sulphamoyl, N,N-(C₁₋₁₀alkyl)₂sulphamoyl, N-(C₁₋₁₀alkyl)sulphamoylamino,

25 N,N-(C₁₋₁₀alkyl)₂sulphamoylamino, carbocyclyl, carbocyclylC₁₋₁₀alkyl, heterocyclyl, heterocyclylC₁₋₁₀alkyl, carbocyclyl-(C₁₋₁₀alkylene)_p-R²⁷-(C₁₋₁₀alkylene)_q- or heterocyclyl-(C₁₋₁₀alkylene)_r-R²⁸-(C₁₋₁₀alkylene)_s-; wherein R¹⁴ may be optionally substituted on carbon by one or more substituents selected from R²⁹; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R³⁰; or R¹⁴ is a group of formula (IC):

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R^{15} is hydrogen or C_{1-6} alkyl;

R^{16} is hydrogen or C_{1-6} alkyl; wherein R^{16} may be optionally substituted on carbon by
5 one or more groups selected from R^{31} ;

n is 1-3; wherein the values of R^7 may be the same or different;

$R^{17}, R^{18}, R^{19}, R^{23}, R^{25}, R^{29}$ or R^{31} are independently selected from halo, nitro, cyano,
hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C_{1-10} alkyl,
 C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy, C_{1-10} alkanoyl, C_{1-10} alkanoyloxy, $N-(C_{1-10}$ alkyl)amino,
10 $N,N-(C_{1-10}$ alkyl)₂amino, $N,N,N-(C_{1-10}$ alkyl)₃ammonio, C_{1-10} alkanoylamino,
 $N-(C_{1-10}$ alkyl)carbamoyl, $N,N-(C_{1-10}$ alkyl)₂carbamoyl, C_{1-10} alkylS(O)_a wherein a is 0 to 2,
 $N-(C_{1-10}$ alkyl)sulphamoyl, $N,N-(C_{1-10}$ alkyl)₂sulphamoyl, $N-(C_{1-10}$ alkyl)sulphamoylamino,
 $N,N-(C_{1-10}$ alkyl)₂sulphamoylamino, C_{1-10} alkoxycarbonylamino, carbocyclyl,
carbocyclyl C_{1-10} alkyl, heterocyclyl, heterocyclyl C_{1-10} alkyl,
15 carbocyclyl-(C_{1-10} alkylene)_p- R^{32} -(C_{1-10} alkylene)_q- or
heterocyclyl-(C_{1-10} alkylene)_r- R^{33} -(C_{1-10} alkylene)_s; wherein $R^{17}, R^{18}, R^{19}, R^{23}, R^{25}, R^{29}$ or R^{31}
may be independently optionally substituted on carbon by one or more R^{34} ; and wherein if
said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a
group selected from R^{35} ;

20 $R^{21}, R^{22}, R^{27}, R^{28}, R^{32}$ or R^{33} are independently selected from -O-, -NR³⁶-, -S(O)_x-,
-NR³⁶C(O)NR³⁶-, -NR³⁶C(S)NR³⁶-, -OC(O)N=C-, -NR³⁶C(O)- or -C(O)NR³⁶-, wherein R³⁶ is
selected from hydrogen or C_{1-6} alkyl, and x is 0-2;

p, q, r and s are independently selected from 0-2;

25 R^{34} is selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carbamoyl,
mercапто, sulphamoyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy,
vinyl, allyl, ethynyl, formyl, acetyl, formamido, acetylarnino, acetoxy, methylarnino,
dimethylarnino, N -methylcarbamoyl, N,N -dimethylcarbamoyl, methylthio, methylsulphinyl,
mesyl, N -methylsulphamoyl, N,N -dimethylsulphamoyl, N -methylsulphamoylarnino and
 N,N -dimethylsulphamoylarnino;

- 10 -

R^{20} , R^{24} , R^{26} , R^{30} or R^{35} are independently selected from C_{1-6} alkyl, C_{1-6} alkanoyl, C_{1-6} alkylsulphonyl, C_{1-6} alkoxycarbonyl, carbamoyl, $N-(C_{1-6}$ alkyl)carbamoyl, $N,N-(C_{1-6}$ alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

5 In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. For example, " C_{1-6} alkyl" includes C_{1-4} alkyl, C_{1-3} alkyl, propyl, isopropyl and *t*-butyl. However, references to individual alkyl groups such as 'propyl' are specific for the straight chained version only and references to individual branched chain alkyl groups
10 such as 'isopropyl' are specific for the branched chain version only. A similar convention applies to other radicals, for example "phenyl C_{1-6} alkyl" would include phenyl C_{1-6} alkyl, benzyl, 1-phenylethyl and 2-phenylethyl. The term "halo" refers to fluoro, chloro, bromo and iodo.

15 Where optional substituents are chosen from "one or more" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

"Heteroaryl" is a totally unsaturated, mono or bicyclic ring containing 3-12 atoms of which at least one atom, particularly 1-3 atoms, are chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked. Preferably "heteroaryl" 20 refers to a totally unsaturated, monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked. Examples and suitable values of the term "heteroaryl" are thienyl, isoxazolyl, imidazolyl, pyrrolyl, thiadiazolyl, isothiazolyl, triazolyl, pyranyl, indolyl, pyrimidyl, pyrazinyl, pyridazinyl, pyridyl 25 and quinolyl. Preferably the term "heteroaryl" refers to thienyl or indolyl. "Heteroaryl" is not tetrazolyl.

30 "Aryl" is a totally unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms. Preferably "aryl" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Suitable values for "aryl" include phenyl or naphthyl. Particularly "aryl" is phenyl.

A "heterocycl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 3-12 atoms of which at least one atom, particularly 1-3 atoms, are chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen

linked, wherein a -CH₂- group can optionally be replaced by a -C(O)- or a ring sulphur atom may be optionally oxidised to form the S-oxides. Preferably a "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise

- 5 specified, be carbon or nitrogen linked, wherein a -CH₂- group can optionally be replaced by a -C(O)- or a ring sulphur atom may be optionally oxidised to form S-oxide(s). Examples and suitable values of the term "heterocyclyl" are thiazolidinyl, pyrrolidinyl, pyrrolinyl, 2-pyrrolidonyl, 2,5-dioxopyrrolidinyl, 2-benzoxazolinonyl, 1,1-dioxotetrahydrothienyl, 2,4-dioxoimidazolidinyl, 2-oxo-1,3,4-(4-triazolinyl), 2-oxazolidinonyl, 5,6-dihydouracilyl,
- 10 1,3-benzodioxolyl, 1,2,4-oxadiazolyl, 2-azabicyclo[2.2.1]heptyl, 4-thiazolidinyl, morpholino, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, 2,3-dihydrobenzofuranyl, benzothienyl, tetrahydropyranlyl, piperidyl, 1-oxo-1,3-dihydroisoindolyl, piperazinyl, thiomorpholino, 1,1-dioxothiomorpholino, tetrahydropyranlyl, 1,3-dioxolanyl, homopiperazinyl, thietyl, isoxazolyl, imidazolyl, pyrrolyl, thiadiazolyl, isothiazolyl, 1,2,4-triazolyl, 1,3,4-triazolyl,
- 15 pyranyl, indolyl, pyrimidyl, thiazolyl, pyrazinyl, pyridazinyl, pyridyl, 4-pyridonyl, quinolyl and 1-isoquinolonyl. "Heterocyclyl" is not tetrazolyl.

A "carbocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms; wherein a -CH₂- group can optionally be replaced by a -C(O)-. Preferably "carbocyclyl" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Suitable values for "carbocyclyl" include cyclopropyl, cyclobutyl, 1-oxocyclopentyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, phenyl, naphthyl, tetalinyl, indanyl or 1-oxoindanyl. Particularly "carbocyclyl" is cyclopropyl, cyclobutyl, 1-oxocyclopentyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, phenyl or 1-oxoindanyl.

- 25 An example of "C₁₋₁₀alkanoyloxy" and "C₁₋₆alkanoyloxy" is acetoxy. Examples of "C₁₋₁₀alkoxycarbonyl" and "C₁₋₆alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of "C₁₋₁₀alkoxy" and "C₁₋₆alkoxy" include methoxy, ethoxy and propoxy. Examples of "C₁₋₁₀alkanoylamino" and "C₁₋₆alkanoylamino" include formamido, acetamido and propionylamino. Examples of "C₁₋₁₀alkylS(O)_a wherein a is 0 to 2" and "C₁₋₆alkylS(O)_a wherein a is 0 to 2" include methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of "C₁₋₁₀alkanoyl" and "C₁₋₆alkanoyl" include C₁₋₃alkanoyl, propionyl and acetyl. Examples of "N-C₁₋₁₀alkylamino" and "N-C₁₋₆alkylamino" include methylamino and ethylamino. Examples of
- 30

"*N,N*-(C₁₋₁₀alkyl)₂amino" and "*N,N*-(C₁₋₆alkyl)₂amino" include di-*N*-methylamino, di-(*N*-ethyl)amino and *N*-ethyl-*N*-methylamino. Examples of "C₂₋₁₀alkenyl" and "C₂₋₆alkenyl" are vinyl, allyl and 1-propenyl. Examples of "C₂₋₁₀alkynyl" and "C₂₋₆alkynyl" are ethynyl, 1-propynyl and 2-propynyl. Examples of "*N*-(C₁₋₁₀alkyl)sulphamoyl" and

5 "*N*-(C₁₋₆alkyl)sulphamoyl" are *N*-(C₁₋₃alkyl)sulphamoyl, *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of "*N*-(C₁₋₁₀alkyl)₂sulphamoyl" and "*N*-(C₁₋₆alkyl)₂sulphamoyl" are *N,N*-(dimethyl)sulphamoyl and

10 *N*-(methyl)-*N*-(ethyl)sulphamoyl. Examples of "*N*-(C₁₋₁₀alkyl)carbamoyl" and "*N*-(C₁₋₆alkyl)carbamoyl" are methylaminocarbonyl and ethylaminocarbonyl. Examples of "

15 "*N,N*-(C₁₋₁₀alkyl)₂carbamoyl" and "*N,N*-(C₁₋₆alkyl)₂carbamoyl" are dimethylaminocarbonyl and methylethylaminocarbonyl. Example of "C₁₋₁₀alkylsulphonyl" and "C₁₋₆alkylsulphonyl" are mesyl and ethylsulphonyl. Examples of "*N,N,N*-(C₁₋₁₀alkyl)₃ammonio" and "*N,N,N*-(C₁₋₆alkyl)₃ammonio" are trimethylamino and methyldiethylamino. Examples of "C₁₋₁₀alkoxycarbonylamino" and "C₁₋₆alkoxycarbonylamino" are methoxycarbonylamino and

20 *t*-butoxycarbonylamino. Examples of "*N*-(C₁₋₁₀alkyl)sulphamoylamino" and "*N*-(C₁₋₆alkyl)sulphamoylamino" are *N*-methylsulphamoylamino and *N*-ethylsulphamoylamino. Examples of "*N,N*-(C₁₋₁₀alkyl)₂sulphamoylamino" and "*N,N*-(C₁₋₆alkyl)₂sulphamoylamino" are *N*,*N*-dimethylsulphamoylamino and *N*-methyl-*N*-ethylsulphamoylamino. Examples of "C₁₋₁₀alkylthio" and "C₁₋₆alkylthio" are methylthio and ethylthio. Examples of "carbocyclylC₁₋₁₀alkyl" include benzyl and phenethyl. Examples of "heterocyclylC₁₋₁₀alkyl" include morpholinopropyl and pyridylmethyl.

A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric, acetate or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

The compounds of the formula (I) may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the formula (I).

examples of pro-drugs include *in vivo* hydrolysable esters and *in vivo* hydrolysable amides of a compound of the formula (I).

An *in vivo* hydrolysable ester of a compound of the formula (I) containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the 5 human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C₁₋₆alkoxymethyl esters for example methoxymethyl, C₁₋₆alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C₃₋₈cycloalkoxycarbonyloxyC₁₋₆alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and 10 C₁₋₆alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

An *in vivo* hydrolysable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and α -acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the 15 parent hydroxy group. Examples of α -acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and 20 carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzoyl ring.

A suitable value for an *in vivo* hydrolysable amide of a compound of the formula (I) containing a carboxy group is, for example, a N-C₁₋₆alkyl or N,N-di-C₁₋₆alkyl amide such as N-methyl, N-ethyl, N-propyl, N,N-dimethyl, N-ethyl-N-methyl or N,N-diethyl amide.

25 Some compounds of the formula (I) may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers that possess IBAT inhibitory activity.

The invention relates to any and all tautomeric forms of the compounds of the formula (I) that possess IBAT inhibitory activity.

30 It is also to be understood that certain compounds of the formula (I) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be

understood that the invention encompasses all such solvated forms which possess IBAT inhibitory activity.

Particular values are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

5 R^y is selected from hydrogen.
R¹ and R² are both C₁₋₆alkyl.
R¹ and R² are both C₁₋₄alkyl.
One of R¹ and R² is ethyl and the other is butyl.
R¹ and R² are both butyl.

10 R^x and R^y are both hydrogen.
R^z is C₁₋₄alkyl.
v is 0-2.
v is 0.
R⁴ is a group of formula (IA).

15 R⁵ is a group of formula (IA).
R³ and R⁶ are hydrogen.
R⁴ is halo.
R⁴ is bromo or chloro.
R⁴ is C₁₋₆alkoxy.

20 R⁴ is ethoxy or methoxy.
R⁴ is methoxy.
R⁴ is ethylthio or methylthio.
R⁴ is methylthio.
R⁵ is methylthio.

25 R⁵ is a group of formula (IA) and R⁴ is C₁₋₆alkylS(O)_a wherein a is 0.
R⁵ is a group of formula (IA) and R⁴ is C₁₋₄alkylS(O)_a wherein a is 0.
R⁵ is a group of formula (IA) and R⁴ is methylthio.
X is -O-.

Ring A is aryl; wherein Ring A is optionally substituted on carbon by one or more substituents selected from R¹⁸, wherein R¹⁸ is hydroxy.

30 Ring A is phenyl; wherein Ring A is optionally substituted on carbon by one or more substituents selected from R¹⁸; wherein R¹⁸ is hydroxy.

Ring A is phenyl or 4-hydroxyphenyl.

R⁷ is hydrogen.

R⁸ is hydrogen.

R⁹ is hydrogen.

5 R¹⁰ is a group of formula (IB).

R¹¹ is hydrogen.

R¹² and R¹³ are independently selected from hydrogen or C₁₋₁₀alkyl.

R¹² and R¹³ are independently selected from hydrogen or C₁₋₄alkyl.

R¹² and R¹³ are independently selected from hydrogen or methyl.

10 R¹² and R¹³ are both hydrogen or one of R¹² and R¹³ is hydrogen and the other is methyl.

R¹⁴ is selected from C₁₋₁₀alkyl or carbocycl[C₁₋₁₀alkyl]; wherein R¹⁴ may be optionally substituted on carbon by one or more substituents selected from R²⁹; wherein R²⁹ is hydroxy.

15 R¹⁴ is selected from C₁₋₁₀alkyl, carbocycl[C₁₋₁₀alkyl] and heterocycl[C₁₋₁₀alkyl]; wherein R¹⁴ may be optionally substituted on carbon by one or more substituents selected from R²⁹; wherein R²⁹ is hydroxy; or R¹⁴ is a group of formula (IC) (as depicted above).

R¹⁴ is selected from C₁₋₆alkyl or phenylC₁₋₄alkyl; wherein R¹⁴ may be optionally substituted on carbon by one or more substituents selected from R²⁹; wherein R²⁹ is hydroxy.

20 R¹⁴ is selected from pentyl, benzyl and tetrahydropyran; wherein R¹⁴ may be optionally substituted on carbon by one or more substituents selected from R²⁹; wherein R²⁹ is hydroxy; or R¹⁴ is a group of formula (IC) (as depicted above).

R¹⁴ is selected from pentyl or benzyl; wherein R¹⁴ may be optionally substituted on carbon by one or more substituents selected from R²⁹; wherein R²⁹ is hydroxy.

R¹⁴ is selected from 1,2,3,4,5-pentahydroxypentyl or 3,4-dihydroxybenzyl.

25 R¹⁵ and R¹⁶ together with the nitrogen to which they are attached form a heterocycl; wherein said heterocycl may be optionally substituted on carbon by one or more R³⁷; wherein R³⁷ is N-(C₁₋₁₀alkyl)carbamoyl; optionally substituted on carbon by one or more R³⁴; wherein R³⁴ is carbamoyl.

R¹⁵ and R¹⁶ together with the nitrogen to which they are attached form pyrrolidinyl; wherein said pyrrolidinyl may be optionally substituted on carbon by one or more R³⁷; R³⁷ is N-methylcarbamoyl; optionally substituted on carbon by one or more R³⁴; wherein R³⁴ is carbamoyl.

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R¹⁵ and R¹⁶ together with the nitrogen to which they are attached form 2-(N-(carbamoylmethyl)carbamoylpyrrolidin-1-yl).

n is 1.

R⁵ is a group of formula (IA) as depicted above wherein:

5 X is -O-;

R⁷ is hydrogen;

R⁸ is hydrogen;

R⁹ is hydrogen;

Ring A is aryl;

10 R¹⁰ is carbamoyl or N-(C₁₋₁₀alkyl)carbamoyl or a group of formula (IB) (as depicted above) wherein R¹⁰ is optionally substituted on carbon by one or more substituents selected from R²³ and wherein:

R¹¹ is hydrogen;

R¹² and R¹³ are independently selected from hydrogen, carbamoyl or C₁₋₆alkyl;

15 wherein R¹² and R¹³ may be independently optionally substituted on carbon by one or more substituents selected from R²⁵;

20 R¹⁴ is selected from carbamoyl, hydroxyaminocarbonyl, C₁₋₆alkyl, carbocyclyl, carbocyclylC₁₋₁₀alkyl, heterocyclyl, heterocyclylC₁₋₁₀alkyl or carbocyclyl-(C₁₋₆alkylene)_p-R²⁷-(C₁₋₆alkylene)_q; wherein R¹⁴ may be optionally substituted on carbon by one or more substituents selected from R²⁹; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R³⁰; or R¹⁴ is a group of formula (IC) (as depicted above) wherein:

R¹⁵ is hydrogen or C₁₋₆alkyl;

25 R¹⁶ is C₁₋₆alkyl; wherein R¹⁶ may be optionally substituted on carbon by one or more groups selected from R³¹;

n is 1;

R²³ is hydroxy;

30 R²⁵, R²⁹ or R³¹ are independently selected from halo, hydroxy, amino, sulphamoyl, C₁₋₆alkoxy, N,N,N-(C₁₋₆alkyl)₃ammonio, N,N-(C₁₋₆alkyl)₂sulphamoylamino, C₁₋₆alkoxycarbonylamino, carbocyclyl, heterocyclyl, carbocyclyl-(C₁₋₆alkylene)_p-R³²-(C₁₋₆alkylene)_q- or heterocyclyl-(C₁₋₆alkylene)_r-R³³-(C₁₋₆alkylene)_s-; wherein R²⁵, R²⁹ or R³¹ may be independently optionally substituted on carbon by one or more R³⁴; and wherein if said

heterocycl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R³⁵;

R²⁷, R³² or R³³ are independently selected from -O-, -NR³⁶C(O)NR³⁶-, -OC(O)N=C- or -NR³⁶C(O)-; wherein R²³ is hydrogen;

5 p, q, r and s are independently selected from 0 or 1;

R³⁴ is selected from hydroxy, amino, carbamoyl, sulphamoyl or methoxy;

R³⁰ or R³⁵ are independently selected from C₁₋₆alkyl or C₁₋₆alkoxycarbonyl.

R⁵ is a group of formula (IA) as depicted above wherein:

X is -O-;

10 Ring A is aryl; wherein Ring A is optionally substituted on carbon by one or more substituents selected from R¹⁸;

R⁷ is hydrogen;

R⁸ is hydrogen;

R⁹ is hydrogen;

15 R¹⁰ is a group of formula (IB) (as depicted above):

R¹¹ is hydrogen;

R¹² and R¹³ are independently selected from hydrogen or C₁₋₁₀alkyl;

R¹⁴ is selected from C₁₋₁₀alkyl, carbocyclC₁₋₁₀alkyl and heterocycl; wherein R¹⁴ may be optionally substituted on carbon by one or more substituents selected from R²⁹; or R¹⁴ is a group of formula (IC) (as depicted above);

20 R¹⁵ and R¹⁶ together with the nitrogen to which they are attached form a heterocycl; wherein said heterocycl may be optionally substituted on carbon by one or more R³⁷;

n is 1;

R¹⁸, R²⁹ and R³⁷ are independently selected from hydroxy and

25 N-(C₁₋₁₀alkyl)carbamoyl; wherein R¹⁸, R²⁹ and R³⁷ may be independently optionally substituted on carbon by one or more R³⁴; and

R³⁴ is carbamoyl.

R⁵ is a group of formula (IA) as depicted above wherein:

X is -O-;

30 R⁷ is hydrogen;

R⁸ is hydrogen;

R⁹ is hydrogen;

Ring A is phenyl;

R¹⁰ is carbamoyl or a group of formula (IB) (as depicted above) wherein:

R¹¹ is hydrogen;

R¹² and R¹³ are independently selected from hydrogen, carbamoyl or C₁₋₆alkyl;

5 wherein R¹² and R¹³ may be independently optionally substituted on carbon by one or more substituents selected from R²⁵;

R¹⁴ is selected from carbamoyl, hydroxyaminocarbonyl, C₁₋₆alkyl, carbocyclyl, heterocyclyl or carbocyclyl-(C₁₋₆alkylene)_p-R²⁷-(C₁₋₆alkylene)_q-; wherein R¹⁴ may be optionally substituted on carbon by one or more substituents selected from R²⁹; and wherein if

10 said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R³⁰; or R¹⁴ is a group of formula (IC) (as depicted above) wherein:

R¹⁵ is hydrogen;

R¹⁶ is C₁₋₆alkyl; wherein R¹⁶ may be optionally substituted on carbon by one or more groups selected from R³¹;

15 n is 1;

R²⁵, R²⁹ or R³¹ are independently selected from halo, hydroxy, amino, sulphamoyl, C₁₋₆alkoxy, N,N,N-(C₁₋₆alkyl)₃ammonio, N,N-(C₁₋₆alkyl)₂sulphamoylamino, C₁₋₆alkoxycarbonylamino, carbocyclyl, heterocyclyl, carbocyclyl-(C₁₋₆alkylene)_p-R³²-(C₁₋₆alkylene)_q- or

20 heterocyclyl-(C₁₋₆alkylene)_r-R³³-(C₁₋₆alkylene)_s-; wherein R²⁵, R²⁹ or R³¹ may be independently optionally substituted on carbon by one or more R³⁴; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R³⁵;

R²⁷, R³² or R³³ are independently selected from -O-, -NR³⁶C(O)NR³⁶-, -OC(O)N=C-

25 or -NR³⁶C(O)-; wherein R²³ is hydrogen;

p, q, r and s are independently selected from 0 or 1;

R³⁴ is selected from hydroxy, amino, carbamoyl, sulphamoyl or methoxy;

R³⁰ or R³⁵ are independently selected from C₁₋₆alkyl or C₁₋₆alkoxycarbonyl.

R⁵ is a group of formula (IA) as depicted above wherein:

30 X is -O-;

R⁷ is hydrogen;

R⁸ is hydrogen;

R⁹ is hydrogen;

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R¹⁰ is carbamoyl or a group of formula (IB) (as depicted above) wherein:

R¹¹ is hydrogen;

R¹² and R¹³ are independently selected from hydrogen, carbamoyl or methyl; wherein R¹² and R¹³ may be independently optionally substituted on carbon by one or more substituents selected from R²⁵;

5 R¹⁴ is selected from carbamoyl, hydroxyaminocarbonyl, methyl, ethyl, propyl, phenyl, 1,5-benzodioxepinyl, 2,3-dihydrobenzofuranyl, piperidinyl, anilinocarbonyl or anilinocarbonyl; wherein R¹⁴ may be optionally substituted on carbon by one or more substituents selected from R²⁹; and wherein said piperidinyl may be optionally substituted on 10 nitrogen by a group selected from R³⁰; or R¹⁴ is a group of formula (IC) (as depicted above) wherein:

R¹⁵ is hydrogen;

15 R¹⁶ is methyl, ethyl or hexyl; wherein R¹⁶ may be optionally substituted on carbon by one or more groups selected from R³¹;

n is 1;
R²⁵, R²⁹ or R³¹ are independently selected from fluoro, hydroxy, amino, sulphamoyl, methoxy, N,N,N-trimethylamino, N,N-dimethylsulphamoylamino, t-butoxycarbonylamino, phenyl, morpholino, imidazolyl, indolyl, 2,4-thiazolidinedionyl, piperazinyl, 2-imidazolidinonyl, phenoxy, benzyloxycarbonyliminomethyl, N'-pyridinylureido or N'-pyrimidinylureido; wherein R²⁵, R²⁹ or R³¹ may be independently optionally substituted on carbon by one or more R³⁴; and wherein said imidazolyl, indolyl, piperazinyl or 2-imidazolidinonyl may be optionally substituted on nitrogen by a group selected from R³⁵;

20 R²⁷, R³² or R³³ are independently selected from -O-, -NHC(O)NH-, -OC(O)N=C- or -NHC(O)-;

25 p, q, r and s are independently selected from 0 or 1;

R³⁴ is selected from hydroxy, amino, carbamoyl, sulphamoyl or methoxy;

R³⁰ or R³⁵ are independently selected from methyl or C₁₋₆alkoxycarbonyl.

R⁵ is a group of formula (IA) as depicted above wherein:

X is -O-;

30 Ring A is phenyl; wherein Ring A is optionally substituted on carbon by one or more substituents selected from R¹⁸;

R⁷ is hydrogen;

R⁸ is hydrogen;

R^9 is hydrogen;

R^{10} is a group of formula (IB) (as depicted above);

R^{11} is hydrogen;

R^{12} and R^{13} are independently selected from hydrogen or methyl;

5 R^{14} is selected from pentyl, benzyl and tetrahydropyran; wherein R^{14} may be optionally substituted on carbon by one or more substituents selected from R^{29} ; or R^{14} is a group of formula (IC) (as depicted above);

R^{15} and R^{16} together with the nitrogen to which they are attached form pyrrolidinyl; wherein said pyrrolidinyl may be optionally substituted on carbon by one or more R^{37} ;

10 n is 1;

R^{18} , R^{29} and R^{37} are independently selected from hydroxy and *N*-methylcarbamoyl; wherein R^{18} , R^{29} and R^{37} may be independently optionally substituted on carbon by one or more R^{34} ; and

R^{34} is carbamoyl.

15 R^5 is selected from:

N-{(R)- α -[*N*'-(2-hydroxyethyl)carbamoyl]benzyl}carbamoylmethoxy;

N-{(R)- α -[*N*'-(2-trimethylaminoethyl)carbamoyl]benzyl}carbamoylmethoxy;

N-{(R)- α -[*N*'-(2-aminoethyl)carbamoyl]benzyl}carbamoylmethoxy;

N-{(R)- α -[*N*'-(carbamoylmethyl)carbamoyl]benzyl}carbamoylmethoxy;

20 *N*-{(R)- α -[*N*'-((S)-1-carbamoyl-2-hydroxyethyl)carbamoyl]benzyl}carbamoylmethoxy;

N-((R)- α -carbamoylbenzyl)carbamoylmethoxy;

N-{(R)- α -[*N*'-(1,1-di-hydroxymethyl-2-hydroxyethyl)carbamoyl]benzyl}carbamoylmethoxy;

N-{(R)- α -[*N*'-(hydroxycarbamoylmethyl)carbamoyl]benzyl}carbamoylmethoxy;

N-((R)- α -{*N*'-[*N*-(2,2,2-trifluoroethyl)carbamoylmethyl]carbamoyl}benzyl)

25 carbamoylmethoxy;

N-((R)- α -{*N*'-[*N*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoylmethyl]carbamoyl}benzyl)carbamoylmethoxy;

N-((R)- α -{*N*'-[*N*-(2-fluoroethyl)carbamoylmethyl]carbamoyl}benzyl)carbamoylmethoxy;

N-((R)- α -{*N*'-[*N*-(ethyl)carbamoylmethyl]carbamoyl}benzyl)carbamoylmethoxy;

30 *N*-((R)- α -{*N*'-[*N*-(4-hydroxy-3-methoxybenzyl)carbamoylmethyl]carbamoyl}benzyl)carbamoylmethoxy;

N-((R)- α -{*N*'-[*N*-(2-methoxyethyl)carbamoylmethyl]carbamoyl}benzyl)carbamoylmethoxy;

N-((R)- α -{*N'*-[*N*-(4-sulphamoylphenethyl)carbamoylmethyl]carbamoyl}benzyl)carbamoylmethoxy;

N-((R)- α -{*N'*-[*N*-(2-*N,N*-dimethylaminosulphamoylethyl)carbamoylmethyl]carbamoyl}benzyl)carbamoylmethoxy;

5 *N*-[(R)- α -{*N'*-(*N*-[2-(*N*-pyrimidin-2-ylureido)ethyl]carbamoylmethyl]carbamoyl}benzyl]carbamoylmethoxy;

(*N*-{(R)- α -{*N'*-[2-(*S*-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy};

10 *N*-{(R)- α -{*N'*-[3-morpholinopropyl]carbamoyl}benzyl}carbamoylmethoxy;

N-{(R)- α -{*N'*-[2-imidazol-4-ylethyl]carbamoyl}benzyl}carbamoylmethoxy;

N-{(R)- α -{*N'*-[2-(*N,N*-dimethylaminosulphamoylethyl)carbamoyl]benzyl}carbamoylmethoxy;

N-((R)- α -{*N'*-[2-(2-hydroxyphenoxy)ethyl]carbamoyl}benzyl)carbamoylmethoxy;

15 *N*-{(R)- α -{*N'*-[3-hydroxy-1,5-benzodioxepin-3-ylmethyl]carbamoyl}benzyl}carbamoylmethoxy;

N-{(R)- α -{*N'*-[3-*t*-butoxycarbonylaminobenzyl]carbamoyl}benzyl}carbamoylmethoxy;

N-((R)- α -{*N'*-[3-(benzyloxycarbonylimino-1-aminomethyl)benzyl]carbamoyl}benzyl)carbamoylmethoxy;

20 *N*-{(R)- α -{*N'*-[2-(3,4-dihydroxyphenyl)-2-methoxyethyl]carbamoyl}benzyl}carbamoylmethoxy;

N-((R)- α -{*N'*-[2-(5-methoxyindol-3-yl)ethyl]carbamoyl}benzyl)carbamoylmethoxy;

N-((R)- α -{*N'*-[2-(2,5-dioxothiazolidin-1-yl)ethyl]carbamoyl}benzyl)carbamoylmethoxy;

N-((R)- α -{*N'*-[3-(4-methylpiperazin-1-yl)propyl]carbamoyl}benzyl)carbamoylmethoxy;

25 *N*-{(R)- α -{*N'*-[4-sulphamoylphenethyl]carbamoyl}benzyl}carbamoylmethoxy;

N-{(R)- α -{*N'*-[5,6-dimethoxy-2,3-dihydrobenzofuran-2-ylmethyl]carbamoyl}benzyl}carbamoylmethoxy;

N-{(R)- α -{*N'*-[1-*t*-butoxycarbonylpiperidin-4-ylmethyl]carbamoyl}benzyl}carbamoylmethoxy;

30 *N*-{(R)- α -{*N'*-[4-nitroanilinocarbonylmethyl]carbamoyl}benzyl}carbamoylmethoxy;

N-((R)- α -{*N'*-[2-(*N*-pyrimidin-2-ylureido)ethyl]carbamoyl}benzyl)carbamoylmethoxy;

N-((R)- α -{*N'*-[2-(*N*-pyridin-2-ylureido)ethyl]carbamoyl}benzyl)carbamoylmethoxy;

N-((R)- α -{*N'*-[2-(4-carbamoylphenoxy)ethyl]carbamoyl}benzyl)carbamoylmethoxy;

N-((*R*)- α -{*N*'-[2-(2-oxoimidazolidin-1-yl)ethyl]carbamoyl}benzyl)carbamoylmethoxy; and
N-{(*R*)- α -[*N*'-(3-aminobenzyl)carbamoyl]benzyl)carbamoylmethoxy.

*R*⁵ is selected from:

5 *N*-{(*R*)- α -[*N*-(2-(*S*)-3-(*R*)-4-(*R*)-5-(*R*)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}
 carbamoylmethoxy;

10 *N*-{(*R*)- α -[*N*-(2-(*S*)-3-(*R*)-4-(*R*)-5-(*R*)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]-4-
 hydroxybenzyl)carbamoylmethoxy;

15 *N*-(*R/S*)- α -{*N*-[1-(*R*)-2-(*S*)-1-hydroxy-1-(3,4-dihydroxyphenyl)prop-2-yl]carbamoyl}-4-
 hydroxybenzyl)carbamoylmethoxy;

20 *N*-[(*R*)- α -{*N*-{2-(*S*)-[*N*-(carbamoylmethyl) carbamoyl]pyrrolidin-1-
 ylcarbonylmethyl}carbamoyl]benzyl]carbamoylmethoxy;

25 *N*-{(*R*)- α -{*N*-[2-(3,4,5-trihydroxyphenyl)ethyl]carbamoyl}benzyl)carbamoylmethoxy; and
 N-{(*R*)- α -[*N*-{2-(*R*)-3-(*S*)-4-(*S*)-5-(*R*)-3,4,5,6-tetrahydroxytetrahydropyran-2-
 ylmethyl)carbamoyl]benzyl}carbamoylmethoxy.

15 Therefore in a further aspect of the invention there is provided a compound of formula
(I) wherein:

20 *R*^y is selected from hydrogen;

25 *R*¹ and *R*² are both C₁₋₆alkyl;

30 *R*^x and *R*^y are both hydrogen;

35 *v* is 0;

40 *R*³ and *R*⁶ are both hydrogen;

45 *R*⁵ is a group of formula (IA) and *R*⁴ is C₁₋₆alkylS(O)_a wherein *a* is 0;
 X is -O-;

50 Ring A is aryl; wherein Ring A is optionally substituted on carbon by one or more
 substituents selected from *R*¹⁸; wherein *R*¹⁸ is hydroxy;

55 *R*⁷ is hydrogen;

60 *R*⁸ is hydrogen;

65 *R*⁹ is hydrogen;

70 *R*¹⁰ is a group of formula (IB);

75 *R*¹¹ is hydrogen;

80 *R*¹² and *R*¹³ are independently selected from hydrogen or C₁₋₁₀alkyl;

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R¹⁴ is selected from C₁₋₁₀alkyl or carbocyclylC₁₋₁₀alkyl; wherein R¹⁴ may be optionally substituted on carbon by one or more substituents selected from R²⁹; wherein R²⁹ is hydroxy; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in a further aspect of the invention there is provided a compound of formula

5 (I) wherein:

R^v is selected from hydrogen;

R¹ and R² are both C₁₋₆alkyl;

R^x and R^y are both hydrogen;

v is 0;

10 R³ and R⁶ are both hydrogen;

R⁵ is a group of formula (IA) and R⁴ is C₁₋₆alkylS(O)_a wherein a is 0;

X is -O-;

Ring A is aryl; wherein Ring A is optionally substituted on carbon by one or more substituents selected from R¹⁸;

15 R⁷ is hydrogen;

R⁸ is hydrogen;

R⁹ is hydrogen;

R¹⁰ is a group of formula (IB) (as depicted above);

R¹¹ is hydrogen;

20 R¹² and R¹³ are independently selected from hydrogen or C₁₋₁₀alkyl;

R¹⁴ is selected from C₁₋₁₀alkyl, carbocyclylC₁₋₁₀alkyl and heterocyclyl; wherein R¹⁴ may be optionally substituted on carbon by one or more substituents selected from R²⁹; or R¹⁴ is a group of formula (IC) (as depicted above);

25 R¹⁵ and R¹⁶ together with the nitrogen to which they are attached form a heterocyclyl; wherein said heterocyclyl may be optionally substituted on carbon by one or more R³⁷;

n is 1;

R¹⁸, R²⁹ and R³⁷ are independently selected from hydroxy and N-(C₁₋₁₀alkyl)carbamoyl; wherein R¹⁸, R²⁹ and R³⁷ may be independently optionally substituted on carbon by one or more R³⁴; and

30 R³⁴ is carbamoyl;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in another aspect of the invention there is provided a compound of formula (I) wherein:

R^v is selected from hydrogen;

R¹ and R² are both butyl;

5 R^x and R^y are both hydrogen;

v is 0;

R³ and R⁶ are both hydrogen;

R⁵ is a group of formula (IA) and R⁴ is methylthio;

X is -O-;

10 Ring A is phenyl or 4-hydroxyphenyl;

R⁷ is hydrogen;

R⁸ is hydrogen;

R⁹ is hydrogen;

R¹⁰ is a group of formula (IB);

15 R¹¹ is hydrogen;

R¹² and R¹³ are both hydrogen or one of R¹² and R¹³ is hydrogen and the other is methyl;

R¹⁴ is selected from 1,2,3,4,5-pentahydroxypentyl or 3,4-dihydroxybenzyl; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

20 Therefore in another aspect of the invention there is provided a compound of formula (I) wherein:

R^v is selected from hydrogen;

R¹ and R² are both butyl;

R^x and R^y are both hydrogen;

25 v is 0;

R³ and R⁶ are both hydrogen;

R⁵ is a group of formula (IA) and R⁴ is methylthio;

X is -O-;

Ring A is phenyl; wherein Ring A is optionally substituted on carbon by one or more substituents selected from R¹⁸;

30 R⁷ is hydrogen;

R⁸ is hydrogen;

R⁹ is hydrogen;

R¹⁰ is a group of formula (IB) (as depicted above);

R¹¹ is hydrogen;

R¹² and R¹³ are independently selected from hydrogen or methyl;

5 R¹⁴ is selected from pentyl, benzyl and tetrahydropyran; wherein R¹⁴ may be optionally substituted on carbon by one or more substituents selected from R²⁹; or R¹⁴ is a group of formula (IC) (as depicted above);

R¹⁵ and R¹⁶ together with the nitrogen to which they are attached form pyrrolidinyl; wherein said pyrrolidinyl may be optionally substituted on carbon by one or more R³⁷;

10 n is 1;

R¹⁸, R²⁹ and R³⁷ are independently selected from hydroxy and N-methylcarbamoyl; wherein R¹⁸, R²⁹ and R³⁷ may be independently optionally substituted on carbon by one or more R³⁴; and

R³⁴ is carbamoyl;

15 or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in another aspect of the invention there is provided a compound of formula (I) wherein:

R^v is selected from hydrogen;

R¹ and R² are both butyl;

20 R^x and R^y are both hydrogen;

v is 0;

R³ and R⁶ are both hydrogen;

R⁴ is methylthio; and

R⁵ is selected from:

25 N-[(R)-α-[N-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl} carbamoylmethoxy;

N-[(R)-α-[N-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]-4-hydroxybenzyl]carbamoylmethoxy;

30 N-((R/S)-α-{N-[1-(R)-2-(S)-1-hydroxy-1-(3,4-dihydroxyphenyl)prop-2-yl]carbamoyl}-4-hydroxybenzyl)carbamoylmethoxy;

N-[(R)-α-(N-{2-(S)-[N-(carbamoylmethyl) carbamoyl]pyrrolidin-1-ylcarbonylmethyl}carbamoyl)benzyl]carbamoylmethoxy;

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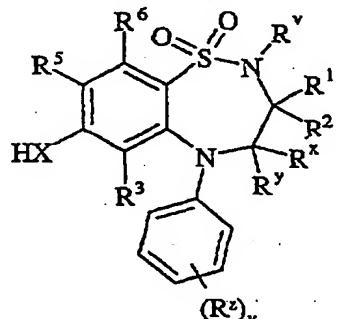
N-(*R*)- α -{*N*-[2-(3,4,5-trihydroxyphenyl)ethyl]carbamoyl}benzyl carbamoylmethoxy; and
N-{(*R*)- α -[*N*-(2-(*R*)-3-(*S*)-4-(*S*)-5-(*R*)-3,4,5,6-tetrahydroxytetrahydropyran-2-ylmethyl]carbamoyl}benzyl carbamoylmethoxy;
or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

5 In another aspect of the invention, preferred compounds of the invention are any one of the examples or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

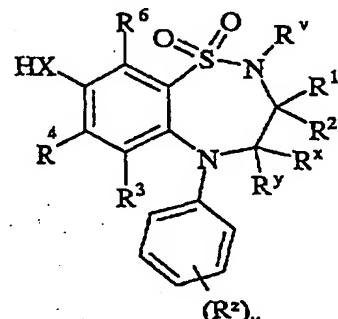
Preferred aspects of the invention are those which relate to the compound of formula (I) or a pharmaceutically acceptable salt thereof.

10 Another aspect of the present invention provides a process for preparing a compound of formula (I) or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof which process (wherein variable groups are, unless otherwise specified, as defined in formula (I)) comprises of:

15 *Process 1*): for compounds of formula (I) wherein X is -O-, -NR^a or -S-; reacting a compound of formula (IIa) or (IIb):

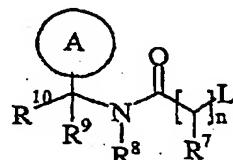


(IIa)



(IIb)

with a compound of formula (III):

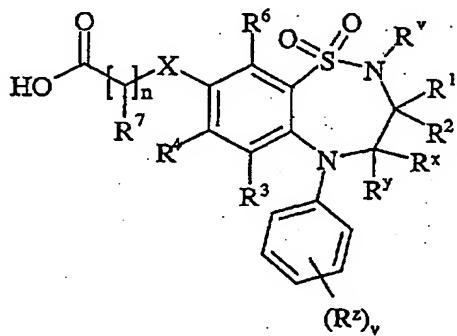


(III)

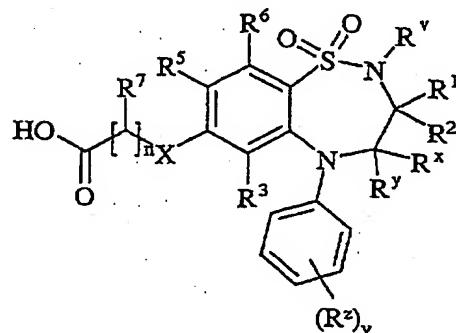
wherein L is a displaceable group;

Process 2): reacting an acid of formula (IVa) or (IVb):

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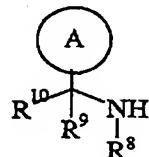


(IVa)



(IVb)

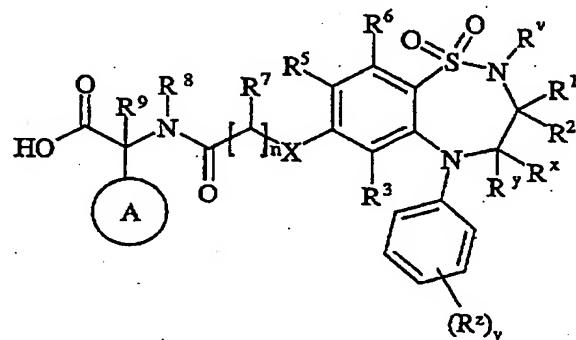
or an activated derivative thereof; with an amine of formula (V):



(V);

5

Process 3): for compounds of formula (I) wherein R^{10} is a group of formula (IB); reacting a compound of formula (VIa):

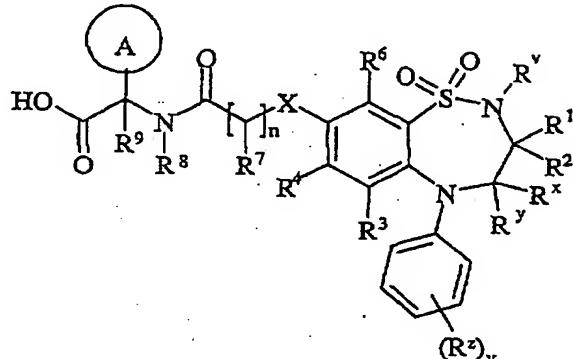


(VIa)

10

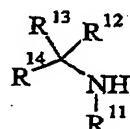
15

or (VIIb):



(VIIb)

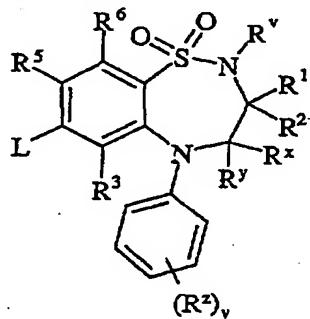
with an amine of formula (VII):



5

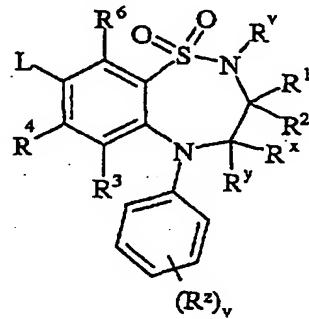
(VII)

Process 4) for compounds of formula (I) wherein one of R⁴ and R⁵ are independently selected from C₁₋₆alkylthio optionally substituted on carbon by one or more R¹⁷; reacting a compound of formula (VIIIa) or (VIIIb):



10

(VIIIa)



(VIIIb)

wherein L is a displaceable group; with a thiol of formula (IX):

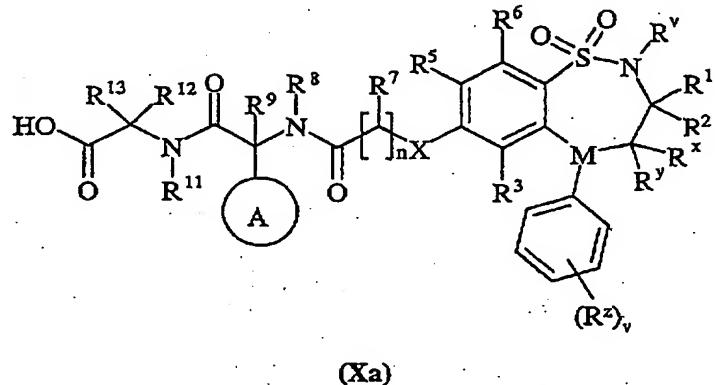


(IX)

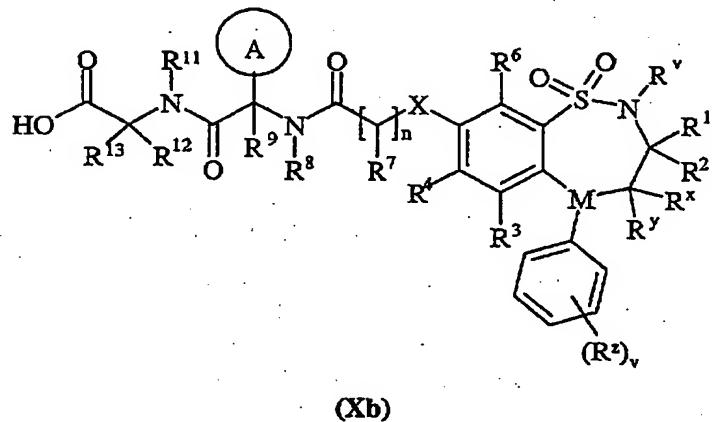
15 wherein R^m is C₁₋₆alkylthio optionally substituted on carbon by one or more R¹⁷; or

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Process 5): for compounds of formula (I) wherein R¹⁴ is a group of formula (IC); reacting a compound of formula (Xa):



5 or (Xb):



with an amine of formula (XI):



10

and thereafter if necessary or desirable:

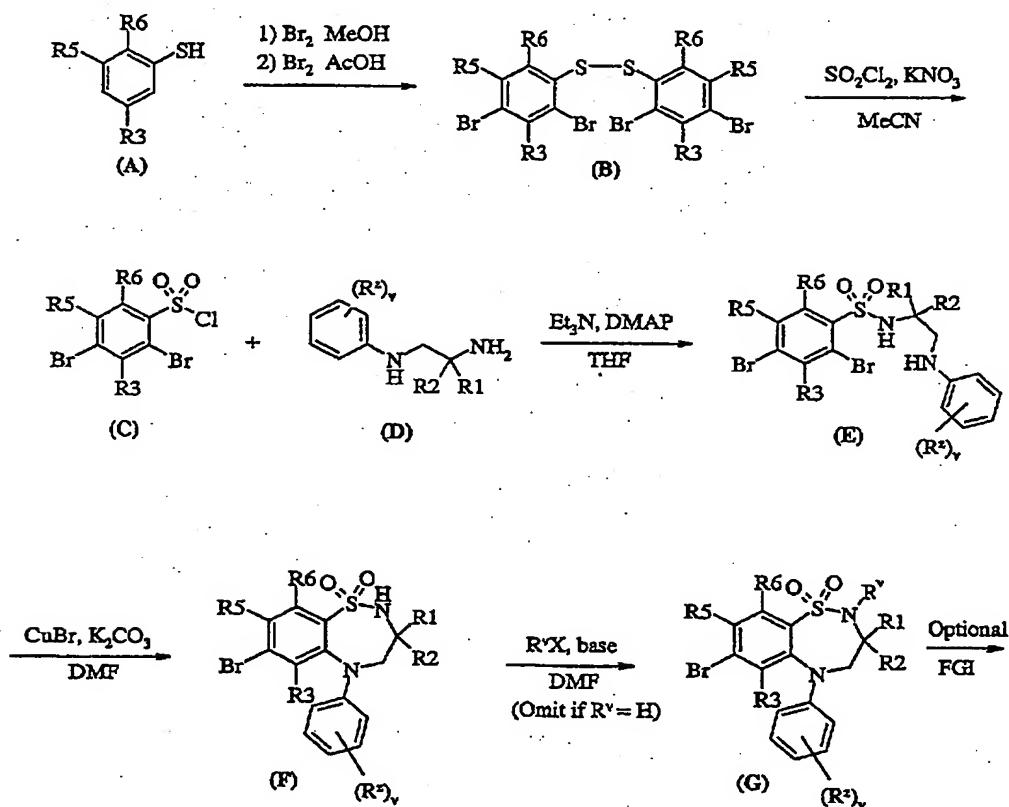
- i) converting a compound of the formula (I) into another compound of the formula (I); and/or
- ii) removing any protecting groups; and/or
- iii) forming a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug.

15

L is a displaceable group, suitable values for L are for example, a halogeno or sulphonyloxy group, for example a chloro, bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group.

Specific reaction conditions for the above reactions are as follows.

The bicyclic ring systems of the present invention may be assembled according the following scheme. The skilled person will appreciate to make any of the above identified intermediates the value of R⁴ or R⁵ in the following schemes would be replaced with the appropriate group. For example, to synthesis a compound of formula (IIa) R⁴ would be HX in the following scheme.



Scheme 1a

FGI is functional interconversion of the Br into other values of R⁴ using procedures known to the skilled person.

Compounds of formula (A) and (D) are commercially available, or they are known in the literature, or they may be prepared by standard processes known in the art.

Process 1: Compounds of formula (IIa) or (IIb) may be reacted with compounds of formula (III) in the presence of a base for example an inorganic base such as sodium carbonate, or an organic base such as Hunigs base, in the presence of a suitable solvent such as acetonitrile,

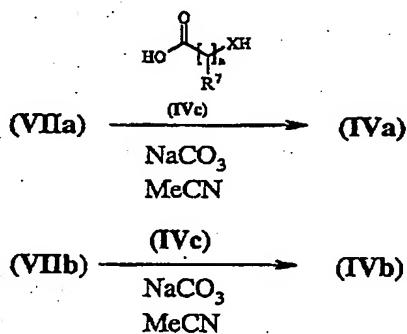
dichloromethane or tetrahydrofuran at a temperature in the range of 0°C to reflux, preferably at or near reflux.

Compounds of formula (III) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

5 *Process 2), Process 3) and Process 5):* Acids and amines may be coupled together in the presence of a suitable coupling reagent. Standard peptide coupling reagents known in the art can be employed as suitable coupling reagents, or for example carbonyldiimidazole and dicyclohexyl-carbodiimide, optionally in the presence of a catalyst such as dimethylaminopyridine or 4-pyrrolidinopyridine, optionally in the presence of a base for 10 example triethylamine, pyridine, or 2,6-di-*alkyl*-pyridines such as 2,6-lutidine or 2,6-di-*tert*-butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran and dimethylformamide. The coupling reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

15 Suitable activated acid derivatives include acid halides, for example acid chlorides, and active esters, for example pentafluorophenyl esters. The reaction of these types of compounds with amines is well known in the art, for example they may be reacted in the presence of a base, such as those described above, and in a suitable solvent, such as those described above. The reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

20 Compounds of formula (IVa) or (IVb) wherein X=-O-, -NR^a, -S- may be prepared according to Scheme 2:

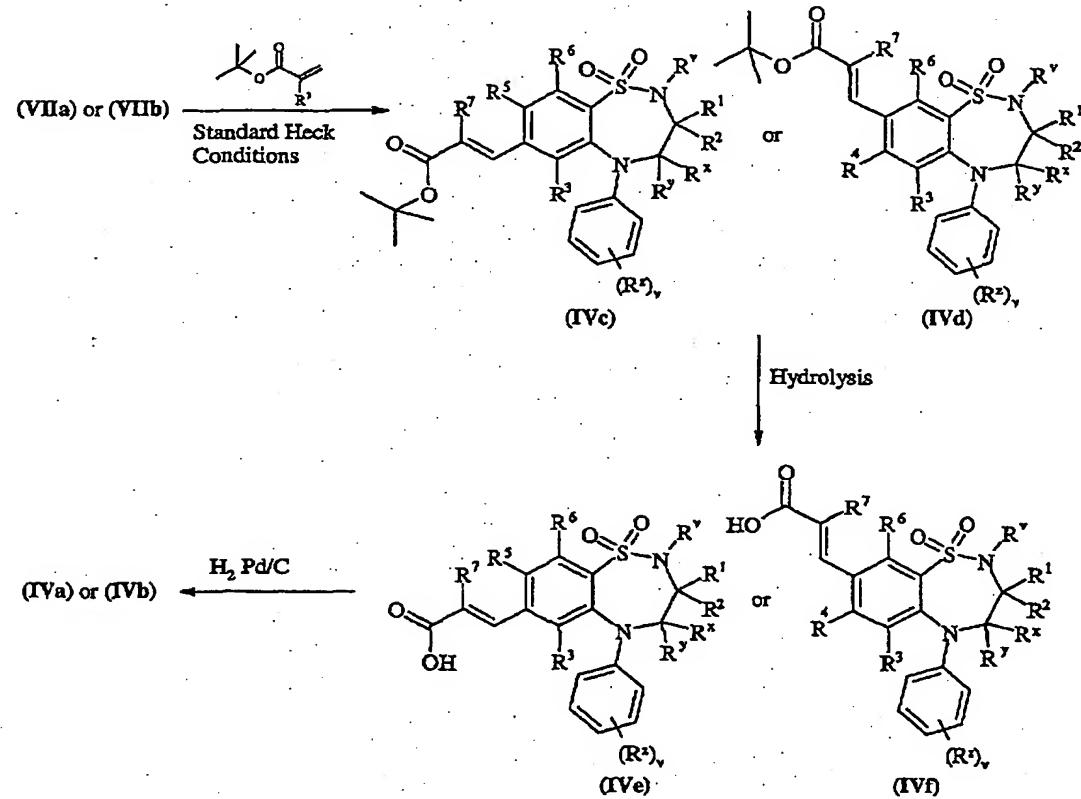


Scheme 2

Wherein L in (VIIa) and (VIIb) is a displaceable group e.g. bromo, chloro, fluoro, 25 mesyl or tosyl and wherein X is -O-, -S-, NR^a (optionally for -SO- and -SO₂- followed by the oxidation step of Process 1).

Compounds of formula (IVa) and (IVb) where X is -SO_2- or $\text{-SO}_2\text{O}-$ may be prepared by oxidising the resulting compounds of formula (IVa) and (IVb) from *Scheme 2* where X is $\text{-S}-$.

Compounds of formula (Va) or (Vb) wherein X is $\text{-CH}_2\text{-}$ may be prepared according to *Scheme 3*.



Scheme 3

Process 4): Compounds of formula (VIIIa) and (VIIIb) may be reacted with thiols of formula (VIII) in the presence of base, for example an inorganic base such as sodium carbonate or an organic base such as Hunigs base, in the presence of a suitable solvent such as DMF or THF 10 at a temperature in the range of 0°C to reflux.

Compounds of formula (VIIIa) and (VIIIb) may be prepared by any of the procedures above for the preparation of compounds of formula (I), but wherein one of R^4 and R^5 is L.

Other starting materials are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

15 It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or

generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation 5 of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group 10 using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyloxy or alkylsulphonyloxy.

15 It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley 20 and Sons, 1999). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, 25 for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such 10 as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis

acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for 5 example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. 10 Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, 15 for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

20 As stated hereinbefore the compounds defined in the present invention possess IBAT inhibitory activity. These properties may be assessed, for example, using an *in vitro* test assay for studying the effect on bile acid uptake in IBAT-transfected cells (Smith L., Price-Jones M. J., Hugues K. T. and Jones N. R. A.; J Biomolecular Screening, 3, 227-230) or *in vivo* by studying the effect on radiolabelled bile acid absorption in mice/rats (Lewis M. C., Brieady 25 L. E. and Root C. J., J Lip Res 1995, 36, 1098-1105).

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

30 The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square meter body area of the animal, i.e. approximately 0.1-100 mg/kg or 0.01-50 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg is employed. In another aspect a daily dose in the range of 0.02-20 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

According to a further aspect of the present invention there is provided a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

We have found that the compounds defined in the present invention, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, are effective IBAT inhibitors, and accordingly have value in the treatment of disease states associated with hyperlipidaemic conditions.

Thus according to this aspect of the invention there is provided a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore for use as a medicament.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of dyslipidemic conditions and disorders such as hyperlipidaemia,

5 hypertriglyceridemia, hyperbetalipoproteinemia (high LDL), hyperprebetalipoproteinemia (high VLDL), hyperchylomicronemia, hypolipoproteinemia, hypercholesterolemia, hyperlipoproteinemia and hypoalphalipoproteinemia (low HDL) in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound
10 of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of different clinical conditions such as atherosclerosis, arteriosclerosis, arrhythmia, hyper-thrombotic conditions, vascular dysfunction, endothelial dysfunction, heart failure, coronary heart diseases, cardiovascular diseases, myocardial infarction, angina pectoris,
15 peripheral vascular diseases, inflammation of cardiovascular tissues such as heart, valves, vasculature, arteries and veins, aneurisms, stenosis, restenosis, vascular plaques, vascular fatty streaks, leukocytes, monocytes and/or macrophage infiltration, intimal thickening, medial thinning, infectious and surgical trauma and vascular thrombosis, stroke and transient ischaemic attacks in a warm-blooded animal, such as man.

20 According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of atherosclerosis, coronary heart diseases, myocardial infarction, angina pectoris, peripheral vascular diseases, stroke and transient ischaemic attacks in a warm-blooded animal,
25 such as man.

According to a further feature of this aspect of the invention there is provided a method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further feature of this aspect of the invention there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need

of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further feature of this aspect of the invention there is provided a
5 method of treating dyslipidemic conditions and disorders such as hyperlipidaemia, hypertriglyceridemia, hyperbetalipoproteinemia (high LDL), hyperprebetalipoproteinemia (high VLDL), hyperchylomicronemia, hypolipoproteinemia, hypercholesterolemia, hyperlipoproteinemia and hypoalphalipoproteinemia (low HDL) in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an
10 effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further feature of this aspect of the invention there is provided a method of treating different clinical conditions such as atherosclerosis, arteriosclerosis, arrhythmia, hyper-thrombotic conditions, vascular dysfunction, endothelial dysfunction, heart
15 failure, coronary heart diseases, cardiovascular diseases, myocardial infarction, angina pectoris, peripheral vascular diseases, inflammation of cardiovascular tissues such as heart, valves, vasculature, arteries and veins, aneurisms, stenosis, restenosis, vascular plaques, vascular fatty streaks, leukocyte, monocytes and/or macrophage infiltrate, intimal thickening, medial thinning, infectious and surgical trauma and vascular thrombosis, stroke and transient
20 ischaemic attacks in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further feature of this aspect of the invention there is provided a method of treating atherosclerosis, coronary heart diseases, myocardial infarction, angina
25 pectoris, peripheral vascular diseases, stroke and transient ischaemic attacks in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

There is evidence that an IBAT inhibitor might potentially be useful in the treatment
30 and/or prevention of gallstones. According to a further feature of this aspect of the invention there is provided a method of treating and / or preventing gallstones in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal

an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

The size of the dose required for the therapeutic or prophylactic treatment will necessarily be varied depending on the host treated, the route of administration and the 5 severity of the illness being treated. A unit dose in the range, for example, 0.02-50 mg/kg, preferably 0.1-100 mg/kg is envisaged..

The IBAT inhibitory activity defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential 10 or separate administration of the individual components of the treatment. According to this aspect of the invention there is provided a pharmaceutical product comprising a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore and an additional IBAT inhibitory substance as defined hereinbefore and an additional hypolipidaemic agent for the conjoint treatment of 15 hyperlipidaemia.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, may be administered in association with an HMG Co-A reductase inhibitor, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable HMG Co-A reductase inhibitors, 20 pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are statins well known in the art. Particular statins are fluvastatin, lovastatin, pravastatin, simvastatin, atorvastatin, cerivastatin, bervastatin, dalvastatin, mevastatin and (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulphonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid (rosuvastatin), or a pharmaceutically acceptable salt, solvate, 25 solvate of such a salt or a prodrug thereof. A particular statin is atorvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A more particular statin is atorvastatin calcium salt. A further particular statin is (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulphonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid (rosuvastatin), or a pharmaceutically acceptable salt, solvate, 30 solvate of such a salt or a prodrug thereof. A preferable particular statin is rosuvastatin calcium salt.

In an additional aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof may be administered in association with an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and/or a bile acid binder thereby avoiding a possible risk of excess of bile acids in colon caused by the inhibition of the ileal bile acid transport system. An excess of bile acids in the visceral contents may cause diarrhoea. Thus, the present invention also provides a treatment of a possible side effect such as diarrhoea in patients during therapy comprising the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

An HMG CoA-reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof will by its action decrease the endogenous cholesterol available for the bile acid synthesis and have an additive effect in combination with the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof on lipid lowering.

Suitable bile acid binders for such a combination therapy are resins, such as cholestyramine and colestipol. One advantage is that the dose of bile acid binder might be kept lower than the therapeutic dose for treatment of cholesterolaemia in single treatment comprising solely a bile acid binder. By a low dose of bile acid binder any possible side effects caused by poor tolerance of the patient to the therapeutic dose could also be avoided.

Therefore in an additional feature of the invention, there is provided a method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with a bile acid binder.

Therefore in an additional feature of the invention, there is provided a method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in simultaneous, sequential or separate administration with a bile acid binder.

Therefore in an additional feature of the invention, there is provided a method of 10 treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, 15 solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of 20 treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of a bile acid binder.

Therefore in an additional feature of the invention, there is provided a method of 25 treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in simultaneous, sequential or separate administration with a bile acid binder.

30 According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an HMG Co-A reductase

inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof and a bile acid binder.

According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;
- b) an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;
- 5 b) a bile acid binder; in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;
- 10 b) an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form;
- c) a bile acid binder; in a third unit dosage form; and
- d) container means for containing said first, second and third dosage forms.

15 According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
- 20 b) an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

- 25 a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
- b) a bile acid binder, in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

30 According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
- 5 b) an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and
- c) a bile acid binder, in a third unit dosage form; and
- d) container means for containing said first, second and third dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder, in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder, in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, a bile acid binder, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder, in the manufacture 5 of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, 10 optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

15 According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of a bile acid 20 binder, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, 25 optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable excipient, with the simultaneous, sequential or separate administration of an effective amount of a bile acid 30 binder, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with 5 the simultaneous, sequential or separate administration one or more of the following agents selected from:

- a CETP (cholesteryl ester transfer protein) inhibitor, for example those referenced and described in WO 00/38725 page 7 line 22 - page 10, line 17 which are incorporated herein by reference;
- 10 ➤ a cholesterol absorption antagonist for example azetidinones such as SCH 58235 and those described in US 5,767,115 which are incorporated herein by reference;
- a MTP (microsomal transfer protein) inhibitor for example those described in Science, 282, 751-54, 1998 which are incorporated herein by reference;
- 15 ➤ a fibrac acid derivative; for example clofibrate, gemfibrozil, fenofibrate, ciprofibrate and bezafibrate;
- a nicotinic acid derivative, for example, nicotinic acid (niacin), acipimox and niacetrol;
- a phytosterol compound for example stanols;
- probucol;
- 20 ➤ an anti-obesity compound for example orlistat (EP 129,748) and sibutramine (GB 2,184,122 and US 4,929,629);
- an antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an adrenergic blocker, an alpha adrenergic blocker, a beta adrenergic blocker, a mixed alpha/beta adrenergic blocker, an adrenergic stimulant, calcium channel blocker, a diuretic or a vasodilator;
- 25 ➤ insulin;
- sulphonylureas including glibenclamide, tolbutamide;
- metformin; and/or
- acarbose;
- 30 or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Particular ACE inhibitors or pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof, including active metabolites, which can be used in combination with a compound of formula (I) include but are not limited to, the following compounds: alacepril, alatriopril, altiopril calcium; ancovenin, benazepril, benazepril hydrochloride, benazeprilat, benzoylcaptopril, captopril, captopril-cysteine, captopril-glutathione, ceranapril, ceranopril, ceronapril, cilazapril, cilazaprilat, delapril, delapril-diacid, enalapril, enalaprilat, enapril, epicaptopril, foroxymithine, fosfenopril, fosenopril, fosenopril sodium, fosinopril, fosinopril sodium, fosinoprilat, fosinoprilic acid, glycopril, hemorphin-4, idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, lyciumin A, lyciumin B, mixanpril, moexipril, moexiprilat, moveltipril, muracein A, muracein B, muracein C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril hydrochloride, quinaprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril, spiropril hydrochloride, temocapril, temocapril hydrochloride, teprotide, trandolapril, trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril and zofenoprilat. Preferred ACE inhibitors for use in the present invention are ramipril, ramiprilat, lisinopril, enalapril and enalaprilat. More preferred ACE inhibitors for uses in the present invention are ramipril and ramiprilat.

Preferred angiotensin II antagonists, pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof for use in combination with a compound of formula (I) include, but are not limited to, compounds: candesartan, candesartan cilexetil, losartan, valsartan, irbesartan, tasosartan, telmisartan and eprosartan. Particularly preferred angiotensin II antagonists or pharmaceutically acceptable derivatives thereof for use in the present invention are candesartan and candesartan cilexetil.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, may be administered in association with a PPAR alpha and/or gamma agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art. These include the compounds described in WO 01/12187, WO 01/12612, WO 99/62870, WO 99/62872, WO 99/62871, WO 98/57941, WO 01/40170, J Med Chem, 1996, 39, 665, Expert Opinion on Therapeutic Patents, 10 (5), 623-634 (in particular the compounds described in the patent applications listed on page 634) and J Med Chem, 2000, 43, 527 which are all incorporated herein by reference. Particularly a PPAR alpha

and/or gamma agonist refers to WY-14643, clofibrate, fenofibrate, bezafibrate, GW 9578, troglitazone, pioglitazone, rosiglitazone, eglitazone, proglitazone, BRL-49634, KRP-297, JTT-501, SB 213068, GW 1929, GW 7845, GW 0207, L-796449, L-165041 and GW 2433. Particularly a PPAR alpha and/or gamma agonist refers to (S)-2-ethoxy-3-[4-(2-{4-methanesulphonyloxyphenyl}ethoxy)phenyl]propanoic acid and pharmaceutically acceptable salts thereof. Additional suitable PPAR alpha and/or gamma agonists are NN622/Ragaglitazar and BMS 298585.

Therefore in an additional feature of the invention, there is provided a method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;
- b) a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and
- 5 c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

- 10 a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
- b) a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

In addition to their use in therapeutic medicine, the compounds of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of IBAT in laboratory animals such 5 as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

Many of the intermediates described herein are novel and are thus provided as a further feature of the invention.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and particular embodiments of the compounds of the 10 invention described herein also apply.

Examples

The invention will now be illustrated in the following non limiting examples, in which standard techniques known to the skilled chemist and techniques analogous to those described in these examples may be used where appropriate, and in which, unless otherwise stated:

15 (i) evaporation were carried out by rotary evaporation in *vacuo* and work up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) all reactions were carried out under an inert atmosphere at ambient temperature, typically in the range 18-25°C, with solvents of HPLC grade under anhydrous conditions, unless otherwise stated;

20 (iii) column chromatography (by the flash procedure) was performed on Silica gel 40-63 µm (Merck);

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the structures of the end products of the formula (I) were generally confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; magnetic 25 resonance chemical shift values were measured in deuterated CD₃OD (unless otherwise stated) on the delta scale (ppm downfield from tetramethylsilane); proton data is quoted unless otherwise stated; spectra were recorded on a Varian Mercury-300 MHz, Varian Unity plus-400 MHz, Varian Unity plus-600 MHz or on Varian Inova-500 MHz spectrometer; and peak multiplicities are shown as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; tt, 30 triple triplet; q, quartet; tq, triple quartet; m, multiplet; br, broad; LCMS were recorded on a Waters ZMD, LC column xTerra MS C₈(Waters), detection with a HP 1100 MS-detector diode array equipped; mass spectra (MS) (loop) were recorded on VG Platform II (Fisons

Instruments) with a HP-1100 MS-detector diode array equipped; unless otherwise stated the mass ion quoted is (MH^+);

(vi) unless further details are specified in the text, analytical high performance liquid chromatography (HPLC) was performed on Prep LC 2000 (Waters), Kromasil C₈, 7μm, (Akzo

5 Nobel); MeCN and de-ionised water 100 mM ammonium acetate as mobile phases, with suitable composition;

(vii) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), HPLC, infra-red (IR), MS or NMR analysis;

(viii) where solutions were dried sodium sulphate was the drying agent;

10 (ix) where an "ISOLUTE" column is referred to, this means a column containing 2 g of silica, the silica being contained in a 6 ml disposable syringe and supported by a porous disc of 54Å pore size, obtained from International Sorbent Technology under the name "ISOLUTE";

"ISOLUTE" is a registered trade mark;

(x) the following abbreviations may be used hereinbefore or hereinafter:-

15	DCM	dichloromethane;
	DMF	N,N-dimethylformamide;
	TBTU	o-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate;
	EtOAc	ethyl acetate;
	MeCN	acetonitrile;
20	TFA	trifluoroacetic acid;
	HATU	o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluoro-
	phosphate; and	
	DIPEA	di-isopropylethylamine.

25 Example 1

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-[(R)-α-[N-(2-(S)-3-(R)-4-(R)-5-(R)-
2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-
benzothiadiazepine

30 A solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)-α-carboxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 1; 0.055 g, 0.086 mmol), D-glucitol, 1-amino-1-deoxy- (0.017 g, 0.094 mmol) and N-methylmorpholine (0.028 ml, 0.254 mmol) in DMF (4 ml) was stirred for 10 min, after which

TBTU (0.033 g, 0.103 mmol) was added. After 18h the solution was diluted with toluene and then concentrated. The residue was purified by preparative HPLC using a gradient of 40-60% MeCN in 0.1M ammonium acetate buffer as eluent. The title compound was obtained in 0.041 g (59 %) as a white solid. NMR (400 MHz, DMSO-d₆): 0.60-0.85 (6H, m), 0.85-1.65 (12H, m), 2.10 (3H, s), 2.95-3.05 (1H, m), 3.20-3.70 (17H (7CH+H₂O), m), 3.85 (2H, bs), 4.20-4.45 (4H, m), 4.60-4.80 (3H, m), 5.55 (1H, d), 6.60 (1H, s), 6.90-7.50 (12H, m), 8.30-8.55 (2H, m); m/z 803.3429.

Example 2

10 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)-α-[N-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]-4-hydroxybenzyl]carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

15 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)-α-carboxy-4-hydroxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 5; 45.5mg, 0.070mmol) was dissolved in 3ml DMF. N-Methylmorpholine (16μl, 0.14mmol) and D-glucamine (16mg, 0.084mmol) were added and the mixture was stirred for 20 min. TBTU (27mg, 0.084mmol) was added and the reaction mixture was stirred overnight. To obtain complete transformation of the starting material, D-glucamine (13.5mg, 0.079mmol), N-methylmorpholine (8μl, 0.070mmol), catalytic amount of tetrabutylammonium bromide and

20 TBTU (3x5mg in portions, 0.04mmol) were added successively. The reaction mixture was concentrated and purified using preparative HPLC on a C8 column (50x250mm) with a gradient (20/80 to 50/50) of MeCN/0.1M ammonium acetate buffer as eluent. The product fraction was concentrated to remove the MeCN and then lyophilized to yield the title compound in 31mg (53% yield). NMR (400MHz): 0.8 (t, 6H), 1.0-1.2 (m, 6H), 1.25-1.4 (m, 2H), 1.4-1.5 (m, 2H), 1.55-1.7 (m, 2H), 2.1 (s, 3H), 3.15-3.25 (m, 1H), 3.45-3.7 (m, 5H), 3.73 (dd, 1H), 3.8-3.85 (m, 1H), 3.95 (brs, 2H), 4.6 (ABq, 2H), 5.3 (s, 1H), 6.6 (s, 1H), 6.75 (d, 2H), 7.05 (t, 1H) 7.15-7.4 (m, 7H); m/z: 819.

Examples 3 and 4

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-(R/S)- α -{N-[1-(R)-2-(S)-1-hydroxy-1-(3,4-dihydroxyphenyl)prop-2-yl]carbamoyl}benzyl]carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine enantiomer 1

5 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-(R/S)- α -{N-[1-(R)-2-(S)-1-hydroxy-1-(3,4-dihydroxyphenyl)prop-2-yl]carbamoyl}benzyl]carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine enantiomer 2

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-(R)- α -carboxybenzyl]carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 1; 50 mg, 0.078 mmol) and 4-[(1R,2S)-2-amino-1-hydroxypropyl]benzene-1,2-diol (17.9 mg, 0.098 mmol) were dissolved in DCM (1ml), DMF (2ml), N-Methylmorpholine (17.2 μ l, 0.156 mmol) and TBTU (45 mg, 0.14 mmol) were added. The reaction mixture was stirred over night and then evaporated under reduced pressure. Proton NMR showed a mixture of two diastereomers due to epimerisation in the phenylglycinresidue. The two diastereomers was separated by preparative HPLC using an acetonitrile/ammonium acetate buffer gradient (5/95 to 100/0) as eluent. The diastereomer that eluted first gave 7 mg (11%) after lyophilisation. NMR (500MHz): 0.81 (brt, 6H), 1.0-1.26 (m, 9H), 1.26-1.41 (m, 2H), 1.42-1.53 (m, 2H), 1.57-1.7 (m, 2H), 2.11 (s, 3H), 3.85-4.2 (m, 3H), 4.33 (d, 1H), 4.65 (ABq, 2H), 5.47 (s, 1H), 6.53 (dd, 1H), 6.57-6.63 (m, 2H), 6.73 (d, 1H), 7.07 (brt, 1H), 7.11-7.17 (m, 2H), 7.18-7.38 (m, 8H); m/z 803.9 (M-H)⁻. The diastereomer eluted second gave 15 mg (24%) after lyophilisation. NMR (500MHz): 0.81 (brt, 6H), 1.0-1.25 (m, 9H), 1.25-1.4 (m, 2H), 1.42-1.52 (m, 2H), 1.57-1.7 (m, 2H), 2.12 (s, 3H), 3.8-4.13 (m, 3H), 4.56-4.74 (m, 3H), 5.47 (s, 1H), 6.61 (brs, 1H), 6.67-6.73 (m, 2H), 6.83 (s, 1H), 7.07 (brt, 1H), 7.15-7.40 (m, 10H); m/z 803.9 (M-H)⁻.

25 Example 5

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-[R)- α -(N-[2-(S)-[N-(carbamoylmethyl)carbamoyl]pyrrolidin-1-ylcarbonylmethyl]carbamoyl)benzyl]carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-(R)- α -carboxybenzyl]carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 1; 46mg, 0.070 mmol) was dissolved in DMF (2ml). (2S)-1-(aminoacetyl)-N-(carbamoylmethyl)pyrrolidine-2-carboxamide (25mg, 0.094 mmol) and N-methylmorpholine (16 μ l, 0.145 mmol) were added.

The solution became cloudy and DMF (1ml) was added. TBTU (21mg, 0.084 mmol) was added in two portions over 10 minutes and the mixture was stirred for 1.5 hours. Formic acid (2 drops) was added after 2 hours. The mixture was purified using preparative HPLC on a C8 column (50x250mm). A step gradient from 20-60% MeCN in 0.1M ammonium acetate buffer was used as eluent. The product fraction was concentrated and lyophilised to yield 22mg (37%). NMR (400 MHz, CD₃OD): 0.79 (t, 6H), 0.98-1.24 (m, 6H), 1.24-1.4 (m, 2H), 1.46 (brt, 2H), 1.55-1.7 (m, 2H), 1.85-2.12 (m, 6H), 2.12-2.24 (m, 1H), 3.4-3.66 (m, 2H), 3.7-4.15 (m, 6H), 4.31-4.37 (m, 1H), 4.63 (ABq, 2H), 5.61 (s, 1H), 6.58 (s, 1H), 7.04 (t, 1H), 7.20 (brd, 2H), 7.24-7.38 (m, 6H), 7.46 (brd, 2H).

10

Example 6

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-(R)-α-{N-[2-(3,4,5-trihydroxyphenyl)ethyl]carbamoyl}benzyl]carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

15

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-(R)-α-carboxybenzyl]carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 1; 60mg, 0.094 mmol), 5-(2-aminoethyl)benzene-1,2,3-triol (25mg, 0.12 mmol) and N-methylmorpholine (21 µl, 0.188 mmol) were dissolved in DMF (2 ml). TBTU (38 mg, 0.12 mmol) was added and the mixture was stirred for 45 minutes. The product was purified by preparative HPLC using a MeCN/ammonium acetate buffer gradient (5/95 to 100/0) as eluent to give the title compound 37 mg (50%). NMR (400 MHz, CD₃OD): 0.79 (t, 6H), 0.95-1.24 (m, 6H), 1.24-1.39 (m, 2H), 1.45 (brt, 2H), 1.54-1.69 (m, 2H), 2.09 (s, 3H), 2.53 (t, 2H), 3.35 (t, 2H), 3.75-4.12 (m, 2H), 4.64 (ABq, 2H), 5.44 (s, 1H), 6.16 (s, 2H), 6.58 (s, 1H), 7.04 (brt, 1H), 7.11-7.45 (m, 10H).

20

Example 7

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-α-[N-(2-(R)-3-(S)-4-(S)-5-(R)-3,4,5,6-tetrahydroxytetrahydropyran-2-ylmethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

25

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-(R)-α-carboxybenzyl]carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 1; 56mg, 0.088 mmol), 3-(R)-4-(S)-5-(S)-6-(R)-2,3,4,5-tetrahydroxy-6-(aminomethyl) tetrahydropyran (25.4 mg, 0.12 mmol) and N-methylmorpholine (19 µl, 0.175 mmol) were dissolved in DMF (2 ml)

and water (10 drops). TBTU (34 mg, 0.105 mmol) was added and the mixture was stirred for 2 hours. More TBTU (22 mg) and 3-(R)-4-(S)-5-(S)-6-(R)-2,3,4,5-tetrahydroxy-6-(aminomethyl)tetrahydropyran (5 mg) were added and stirred for a short period. The product was purified by preparative HPLC using a MeCN/ammonium acetate buffer gradient (5/95 to 100/0) as eluent to give the title compound 39 mg (56%). M/z 799.55 (M-H)⁺.

Preparation of Starting Materials

The starting materials for the Examples above are either commercially available or are readily prepared by standard methods from known materials. For example, the following reactions are an illustration, but not a limitation, of some of the starting materials used in the above reactions.

Method 1

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-(R)- α -carboxybenzyl] carbamoylmethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{N-[{(R)- α -(t-butoxycarbonyl)benzyl] carbamoylmethoxy}-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 2; 762 mg, 1.09 mmol) was dissolved in a mixture of TFA (6.65 ml) and triethylsilane (0.350 ml). The reaction mixture was stirred for one hour and then evaporated under reduced pressure to give the title compound in a quantitative yield (714 mg). NMR (500MHz): 0.8 (brt, 6H), 0.96-1.25 (m, 6H), 1.25-1.4 (m, 2H), 1.42-1.51 (m, 2H), 1.57-1.69 (m, 2H), 2.11 (s, 3H), 3.8-4.15 (m, 2H), 4.66 (ABq, 2H), 5.49-5.53 (m, 1H), 6.61 (s, 1H), 7.06 (t, 1H), 7.18-7.26 (m, 2H), 7.28-7.45 (m, 8H), 8.35 (d, NH); m/z 640.2.

Method 2

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-(R)- α -(t-butoxycarbonyl)benzyl] carbamoylmethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 3; 627 mg, 1.24 mmol) was dissolved in DCM (25 ml), tert-butyl (2R)-amino(phenyl)acetate (308 mg, 1.48 mmol, 2,6-dimethylpyridine (288 μ l, 2.47 mmol) and TBTU (477 mg, 1.48 mmol) were added. The mixture was stirred for 3.5 hours. The reaction mixture was evaporated under reduced pressure. The product was purified using

an Isolute column(10g, silica). The product was eluted with a stepwise gradient using DCM:EtOAc 100:0 then 95:5. Approximately 694mg pure compound was collected. An additional fraction was purified a second time using an Isolute column (10g, silica). The product was eluted with a stepwise gradient using DCM:EtOAc 100:0,95:5 then 90:10. The 5 pure fraction was added to the first fraction yielding 787 mg (91%) of the title compound. NMR (400MHz, CDCl₃) 0.78 (t, 6H), 0.92-1.12 (m, 4H), 1.12-1.46 (m, 6H), 1.54 (s, 9H), 1.58-1.72 (m, 2H), 2.14 (s, 3H), 3.8-4.05 (m, 2H), 4.32 (brs, NH), 4.56 (ABq, 2H), 5.56 (d, 1H), 6.56 (s, 1H), 7.04 (t, 1H), 7.10 (brd, 2H) 7.24-7.42 (m, 8H), 7.84 (d, NH); m/z 694.7 (M-H)⁺.

10

Method 3**1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine**

To a solution of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-ethoxycarbonyl-15 methoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 4; 0.024 g, 4.49*10⁻⁵ mol) in EtOH (3 ml) was added NaOH (0.007 g, 1.80*10⁻⁴ mol) and the mixture was stirred over night. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC using an MeCN / ammonium acetate buffer as eluent and freeze-dried. The title compound was obtained in 0.021 g (92 %) as a white solid. NMR (400 MHz, CD₃OD) 0.70-0.85 (m, 6H), 1.00-1.70 (m, 12H), 2.10 (s, 3H), 3.90 (brs, 2H), 4.55 (s, 2H), 6.60 (s, 1H), 6.90-7.35 (m, 6H).

Method 4**1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine**

To a suspension of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-methoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (prepared according to WO 98/38182; 0.218 g, 5.65*10⁻⁴ mol) in DMF (5 ml) was added NaSMe (0.210 g, 2.83 mmol, 95 %), and the mixture was stirred for 5 hours at 120°C. The solvent was removed under reduced pressure and the residue 30 was partitioned between EtOAc and 0.5 M HCl. The aqueous layer was extracted twice more with EtOAc and the combined organic extracts were dried (MgSO₄) and concentrated. The residue was dissolved in MeCN (7 ml) and ethyl bromoacetate (0.063 ml, 5.65*10⁻⁴ mol), tetrabutylammonium bromide (0.018 g, 5.65*10⁻⁵ mol) and sodium carbonate (0.250 g, 2.36

mmol) were added. The mixture was stirred over night at 80°C. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and 0.5 M HCl. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography on silica gel (Hex:EtOAc-6:1) gave the title compound as a colourless oil 0.024 g (8 %).

5 NMR (400 MHz, $CDCl_3$) 0.70-0.85 (m, 6H), 0.90-1.70 (m, 15H), 2.10 (s, 3H), 3.90 (bs, 2H),
4.20 (bs, 1H), 4.25 (q, 2H), 4.65 (s, 2H), 6.55 (s, 1H), 6.95-7.35 (m, 6H).

Method 5

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-(R)- α -carboxy-4-hydroxybenzyl]carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (Method 3; 295mg, 0.58mmol) was dissolved in 10 ml DCM. 4-(1-(R)-*t*-Butoxycarbonyl-1-aminomethyl)phenol (Method 6; 160mg, 0.72mmol), 2,6-lutidine (140 μ l, 1.20mmol) and TBTU (230mg, 0.72mmol) were added successively. The mixture was 15 stirred for 3h. Additional 4-(1-(R)-*t*-butoxycarbonyl-1-aminomethyl)phenol (Method 6; 10mg, 0.04mmol) was added and stirring was continued for 2h. DCM (20ml) was added and the solution was washed with 5% $NaHCO_3$ (20ml), 0.3M $KHSO_4$ (20ml), brine (20ml) before it was dried and concentrated to a volume of 10 ml. The *tert*-butyl ester of the title compound was confirmed; m/z: 729 (M+18 (NH_4^+)). TFA (1.3ml) was added and the mixture was stirred 20 for 4.5h and concentrated. The crude product was purified by preparative HPLC using a C8 column (50x500mm) and a gradient (40/60 to 70/30 over 40 min) of MeCN/0.1M ammonium acetate buffer as eluent. Lyophilization yielded the title compound in 77.5% (302mg). NMR (400MHz): 0.8 (t, 6H), 1.0-1.2 (m, 6H), 1.25-1.4 (m, 2H), 1.4-1.5 (m, 2H), 1.55-1.7 (m, 2H), 2.1 (s, 3H), 3.95 (brs, 2H), 4.6 (ABq, 2H), 5.3 (s, 1H), 6.6 (s, 1H), 6.75 (d, 2H), 7.05 (t, 1H) 25 7.15-7.4 (m, 7H); m/z: 673 (M+18 (NH_4^+)).

Method 6

4-(1-(R)-*t*-Butoxycarbonyl-1-aminomethyl)phenol

Sulfuric acid (1ml conc.) was added to a solution of D-(R)-4-hydroxyphenylglycine 30 (1.0g, 6.0mmol) in 1,4-dioxane (8ml) placed in a Teflon® flask. The flask was cooled to -78°C and isobutylene (8g, 142.6mmol, condensed at -78°C) was added. The flask was placed in an autoclave at room temperature and stirred for 15h. The autoclave was cooled on ice

before opened. The excess isobutylene was allowed to evaporate and the remaining solution was poured into aqueous NaOH (2M, 20ml) and was extracted with diethyl ether to remove formed by-product. The aqueous phase was slightly acidified to attain pH=10 using 2M HCl and was extracted with diethyl ether (3x75ml). The organic phase was washed with brine, 5 dried and concentrated. The obtained product was recrystallized in diethyl ether/hexane. Mass: 0.55g (41%). NMR (600MHz, CDCl₃): 1.45 (s, 9H), 4.45 (s, 1H), 6.8 (d, 2H), 7.25 (d, 2H); m/z: 224.

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